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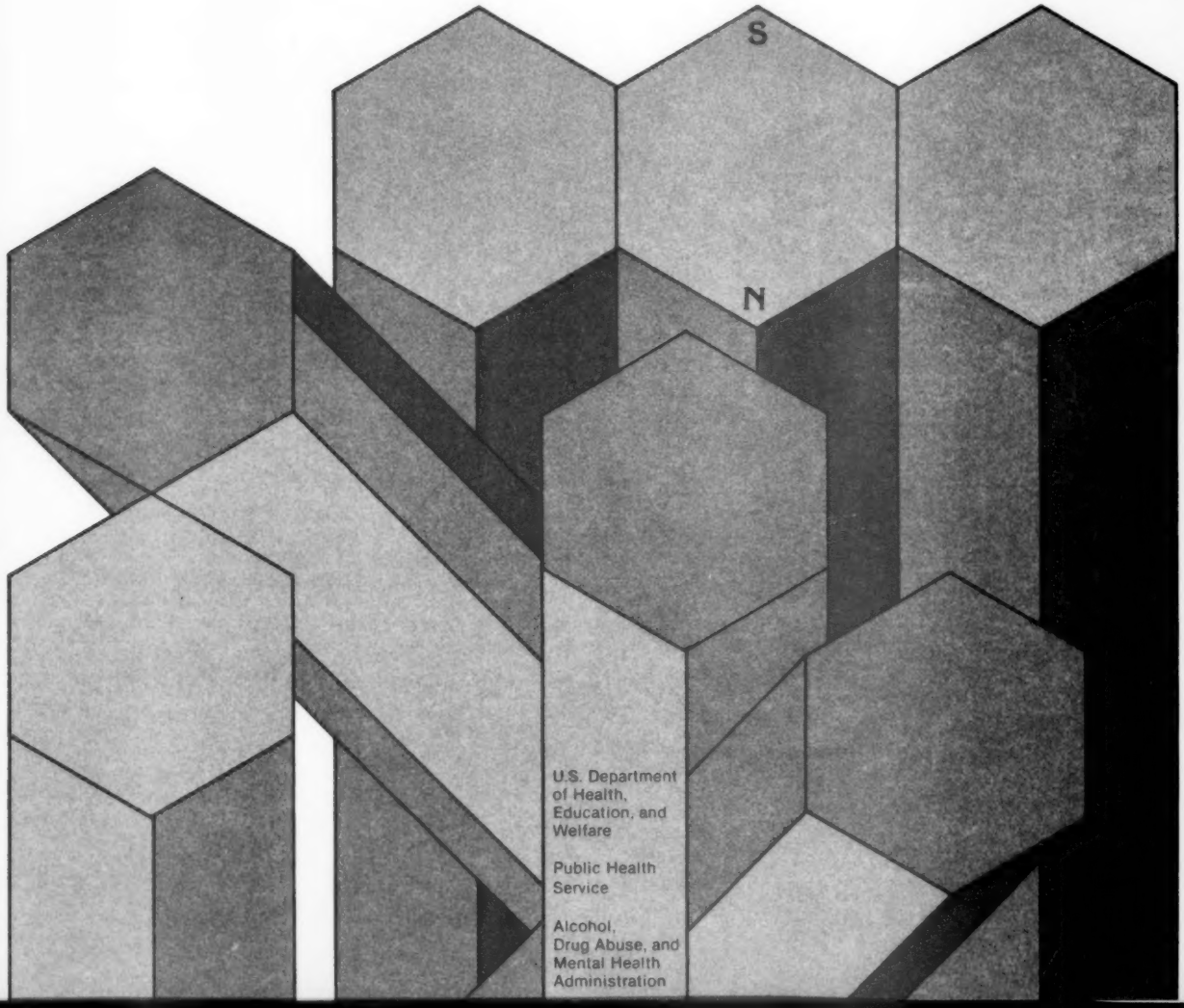

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Carrie Lee Rothgeb, *Editor*
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ABSTRACTS

PRECLINICAL PSYCOPHARMACOLOGY

01 CHEMICAL SYNTHESIS, ISOLATION AND CHARACTERIZATION

003047 Callery, Patrick S.; Leslie, James. School of Pharmacy, University of Maryland, Baltimore, MD 21201 **Thermal decomposition of 1,3-dimethyl derivative of phenobarbital in trimethylanilinium hydroxide.** Journal of Pharmaceutical Sciences. 66(4):578-580, 1977.

The identities of the products resulting from degradation of the 1,3-dimethyl derivative of phenobarbital when the compound is injected with trimethylanilinium hydroxide in methanol into a gas chromatograph were investigated using mass spectrometry. The major products were found to be N-methyl-2-phenylbutyramide, N-N-dimethyl-2-phenylbutyramide, methyl-2-phenylbutyrate, N,N,N′-trimethylethylphenylmalondiamide, and N,N,N′,N′-tetramethylethylphenylmalondiamide. The methyl group of the ester arises from the methanol solvent, whereas the methyl groups of the substituted amides arise from the parent compound or the methylating agent. It was also found that tetramethylammonium hydroxide causes much more degradation of the phenobarbital derivative than does trimethylanilinium hydroxide under comparable conditions. 15 references. (Author abstract modified)

003048 Cardellini, Mario; Claudi, Francesco; Grifantini, Mario; Gulini, Ugo; Martelli, Sante. Istituto di Chimica Farmaceutica e di Chimica Organica, Universita di Camerino, 62032 Camerino (MC), Italia **Indolizine derivatives with biological activity I: N′-substituted hydrazides of indolizine-2-carboxylic acid.** Journal of Pharmaceutical Sciences. 66(2):259-262, 1977.

The synthesis and antimonoamine oxidase (MAO) activity of several N′-substituted hydrazides of indolizine-2-carboxylic acid are described. All of the compounds are MAO inhibitors in vitro and are more active than iproniazid. The structure/activity relationships are also discussed. 15 references. (Author abstract modified)

003049 Chaudhuri, N. K.; Ball, T. J.; Finch, N. Research Dept., Pharmaceuticals Div., Ciba-Geigy Corp., Summit, NJ 07901 **The absolute configuration of SU 23397: a novel neuroleptic agent.** Experientia (Basel). 33(5):575-577, 1977.

The absolute configuration of a novel chiral neuroleptic agent SU 23397 was determined by ORD comparison of (+)-5-methoxy dihydro coumarilic acid, a synthetic precursor of SU 23397, with (+)-dihydro coumarilic acid, whose absolute configuration is known. This assignment was confirmed by oxidative degradation of (+)-5-methoxy dihydro coumarilic acid to D-(+)-malic acid. 14 references. (Author abstract)

003050 Cheung, Alphonsus L.; Stavinoha, W. B.; Goldstein, Avram. Addiction Research Foundation, Palo Alto, CA 94305 **Endorphins in brains of decapitated and microwave-killed mice.** Life Sciences. 20(7):1285-1290, 1977.

The size distribution of opioid peptides (endorphins) in decapitated and microwave killed mice brains was determined by gel filtration, using the inhibition of stereospecific 3H-etorphine binding to guinea pig brain membranes as a measure of endorphin activity. The largest endorphin was about the same size as beta-lipotropin-(61-91), the next largest was about half this size, and the smallest was the size of the pentapeptide enkephalins. There was no important difference in the size distribution between brains of mice killed by the two methods. The results indicate that opioid peptides of all three size classes are present in the brain in vivo. 27 references. (Author abstract modified)

003051 Fuller, Ray W.; Molloy, Bryan B. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206 **Inhibition in vitro of norepinephrine N-methyltransferase by 2-aminotetralins, analogs of phenylethylamines with rigid conformation.** Biochemical Pharmacology (Oxford). 26(5):446-447, 1977.

Several phenylethylamine analogs having a rigid conformation were synthesized, and their ability to inhibit rabbit adrenal gland norepinephrine N-methyltransferase (phenylethanolamine N-methyltransferase, PNMT) was investigated. The bicyclic phenylethylamine derivative containing two six membered rings, 2-aminotetralin (2,3,3,4-tetrahydronamhthalene-2-amine) was found to be the most potent inhibitor of the enzyme, at least 100 fold more active than phenylethylamine, and was subjected to further modification and testing. The addition of a single chlorine atom to any position on the aromatic ring increased inhibitor activity, and the addition of a second chlorine substituent increased inhibitor activity further. The most potent inhibitor studied, 5,6-dichloro-2-aminotetralin, had approximately 10 times the affinity for norepinephrine N-methyltransferase as the most active inhibitor among the previously studied amphetamine series, 3,4-dichloroamphetamine. 10 references.

003052 Grasso, Alfonso; Roda, Giorgio; Hogue-Angeletti, Ruth A.; Moore, Blake W.; Perez, Vernon J. Laboratory of Cell Biology, Rome, Italy **Preparation and properties of the brain specific protein 14-3-2.** Brain Research (Amsterdam). 124(3):497-507, 1977.

The preparation, assay, and physical and chemical characteristics of the brain specific protein 14-3-2 are described, and supporting data establishing organ specificity and species nonspecificity are presented. The protein 14-3-2 was isolated from the bovine brain by the use of ammonium sulfate precipitation, gel filtration on Sephadex G-150, and ion exchange chromatography on DEAE/cellulose and DEAE/Sephadex. It is an acidic protein, in agreement with the high content of glutamic and aspartic acid, that is composed of a single polypeptide chain of molecular weight 50,000. Immunochemical tests using antiserum to purified 14-3-2 showed that the protein is present in at least 100 fold greater amounts in brain than in any other tissue in the rat. Further, 14-3-2 was found in brains of a number of vertebrate species, although the antigen is apparently not entirely identical in all species tested. It is concluded that the protein 14-3-2 can be considered to be a species nonspecific protein that is neuronal in origin. 21 references. (Author abstract modified)

003053 Hulshoff, Abram; Perrin, John H. Pharmaceutical Laboratories, University of Utrecht, Catharijnesingel 60, Utrecht, The Netherlands **Quantitative correlations between albumin binding constants and chromatographic RM values of phenothiazine derivatives.** Journal of Medicinal Chemistry. 20(3):430-439, 1977.

Quantitative correlations between albumin binding constants and chromatographic RM values of 15 phenothiazine deriva-

tives were determined using a circular dichroic probe technique. The lipophilicity of the drugs, measured by a reversed phase thin layer technique using oleyl alcohol and methanol water mixtures as the solvents, is expressed as RMw. The binding constants were of the same order of magnitude as the literature values, and the RMw values correlated well with log Poctanol values from the literature. Correlations of log K with RMw were found to be more satisfactory when corrections for the state of ionization of the phenothiazines were made, the nonprotonated species accounting for the bulk of the binding. A better correlation was obtained when contributions from both species were taken into account. Similar correlations were attempted between RMw values and enzyme inhibitory activities of these phenothiazines taken from the literature. 38 references. (Author abstract modified)

003054 Hyttel, John. Dept. of Pharmacology and Toxicology, H. Lundbeck & Co. A/S, Ottiliavej 7-9, DK-2500 Copenhagen-Valby, Denmark **Neurochemical characterization of a new potent and selective serotonin uptake inhibitor: Lu 10-171.** Psychopharmacology (Berlin). 51(3):225-233, 1977.

The neurochemical characteristics of a new bicyclic phthalane derivative, Lu 10-171, are discussed, and Lu 10-171 and its metabolites are compared with tricyclic thymoleptics in several tests for serotonin (5-HT), noradrenaline (NA), and dopamine (DA) uptake inhibition in vitro and in vivo. Lu 10-171 is a very potent and completely selective inhibitor of the 5-HT reuptake mechanism, being two to 10 times as active as chlorimipramine. The metabolites of Lu 10-171 show weak 5-HT uptake inhibiting properties. Lu 10-171 and its metabolites are devoid of NA uptake inhibiting properties and in this respect they clearly differ from the tricyclic antidepressants. The inhibition of 5-HT uptake in vitro is competitive and not connected with an increased efflux of 5-HT. Lu 10-171 and its metabolites only inhibit DA uptake in extremely high concentrations and, in this respect, they are even weaker than chlorimipramine and other tricyclic thymoleptics. Like the tricyclic thymoleptics, Lu 10-171 is without effect on monoamine oxidase and does not change the endogenous level of brain monoamines. Due to the selective action on 5-HT uptake, Lu 10-171 seems to be a valuable tool in studying the role of cental 5-HT neurone systems in experimental neuropharmacology as well as in the ethiology of depressive illness. 42 references. (Author abstract modified)

003055 Leiby, Robert W.; Heindel, Ned D. Department of Chemistry, Lehigh University, Bethlehem, PA 18015 **New compounds: synthesis of 2-amino-5H-1,3,4-benzotriazepin-5-ones.** Journal of Pharmaceutical Sciences. 66(4):605-606, 1977.

A method for synthesizing 2-amino-5H-1, 3,4-benzotriazepin-5-ones, bioisosteric homologs of the benzodiazepine psychotherapeutic agents which may have sedative activity, is described. The method involves cyclization of anthranilohydrazides in the presence of cyanogen bromide to yield hydrobromide salts of the benzotriazepines. 14 references.

003056 Matsumoto, Ken; Stark, Paul; Meister, Robert G. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206 **Cannabinoids. 2. synthesis and central nervous system activities of some B-ring homocannabinoid derivatives and related lactones.** Journal of Medicinal Chemistry. 20(1):25-30, 1977.

The syntheses of five novel B ring homocannabinoid derivates and related lactones are described. All of the compounds are 6,7,8,9,10,11-hexahydrodibenz(b,d)oxepins. CNS activity/structure correlations were determined by assessing effects on behavior in septal lesioned rats, on muricide behavior in rats and on mouse exploratory behavior. A possible separation of CNS activities was noted with compound 1. Unexpected pharmacological activity was discovered with compound 3, a lactone, which was about equipotent to levo-delta9-tetrahydrocannabinol. Dimethylation at the 7 position decreased CNS activity when the 6 position was a carbonyl group or a methylene group. 12 references. (Author abstract modified)

003057 Melikian, Armen P.; Flynn, Norman W.; Petty, Frederick; Wander, Joseph D. Drug Metabolism Department, Warner-Lambert Research Institute, Morris Plains, NJ 07950 **Chemical ionization mass spectra of phenothiazine derivatives and their oxygenated analogs.** Journal of Pharmaceutical Sciences. 66(2):228-232, 1977.

As part of a continuing program of developing applications of chemical ionization GC-mass spectrometry in neurochemistry, the chemical ionization mass spectra for 29 derivatives of phenothiazine, including chlorpromazine, promazine, promethazine, prochlorperazine, trifluoperazine, perphanazine, fluphenazine and acetophenazine as well as 21 possible or known metabolites of these and related drugs, were investigated. Relatively stable ions were formed by proton capture under conditions of chemical ionization using methane or isobutane as reagent gas. Fragments of generally low abundance were formed by a simple bond cleavage in the trimethylene portion of the side chain and by loss of water or hydrogen halide. Mass spectra obtained from pyrolyzates of amine salts and from the corresponding free bases were essentially identical. 12 references. (Author abstract modified)

003058 Reboul, J.-P.; Cristau. Laboratoire de pharmacie chimique, Faculte de Pharmacie, 27, boulevard Jean Moulin, F-13385 Marseille Cedex 4, France /**Pharmacochemical analysis of radiocrystallographic data on polycyclic psychotropic amines. II. Comparison of the parametric values.**/ Analyse pharmacochimique des donnees fournies par la radiocristallographie des amines psychotropes polycycliques. II. Confrontation des valeurs parametaiques. European Journal of Medicinal Medicine (Paris). 12(1):76-69, 1977.

The values of 16 conformation parameters were tabulated for polycyclic psychotropic amines, the values for neuroleptic phenothiazines were compared to other phenothiazines, and the values for neuroleptics were compared to those of antidepressants. The mean and the standard deviation were tabulated for each parameter for three populations of the drugs: neuroleptics, neuroleptics plus metabolites, and antidepressants, and for delta-p, the ratio of 1.96 times the standard deviation to the mean, was calculated. The neuroleptic phenothiazines chlorpromazine, triflupromazine, thioridazine and thiethylperazine were compared to the antihistaminic and antiparkinsonian phenothiazines promethazine, thiazinamium, diethazine, and isothiazine. The neuroleptics chlorpromazine, triflupromazine, thioridazine, thiethylperazine, alpha-chloroprothixene, alpha-flupenthixole, beta-flupenthixole, and oxyprothepine were compared to the antidepressants imipramine, mianserine, iprindole, and IB-503. The statistical analysis of the parameters indicated no preferred conformation for either class of compound. 4 references.

003059 Reboul, J.-P.; Cristau, B. Laboratoire de Pharmacie Chimique, Faculte de Pharmacie, 27, boulevard Jean Moulin, F-13385 Marseille Cedex 4, France /**Pharmacochemical analysis of radiocrystallographic data of polycyclic psychotropic amines.**

I. Definition and calculation of conformational parameters./ Analyse pharmacochimique des donnees fournies par la radiocristallographie des amines psychotropes polycycliques. I. Definition et calcul des parametres conformationnels. European Journal of Medicinal Chemistry (Paris). 12(1):71-75, 1977.

The definition and calculation of 16 conformational parameters of a series of polycyclic psychotropic amines whose crystal structure had previously been elucidated by x-ray analysis were described. The parameters that permit a quantitative description of the topology of the psychotropic amines were calculated for: 1) the neuroleptics chlorpromazine, triflupromazine, methoxypromazine, thioridazine, thiethylperazine, alpha-chlorprothixene, alpha-flupenthixole, beta-flupenthixole, and oxyprothepine; 2) the antihistamines promethazine and thiazinamium; 3) the antiparkinsonian drugs diethanzine, isothiazine, and methixine; and, 4) the antidepressants imipramine, mianserine, iprindole, and IB 503. Methods for calculation of the parameters were described. 23 references.

003060 Roda, Giorgio; Grasso, Alfonso; Garretto, Silvia; Moore, Blake W.; Hogue-Angeletti, Ruth A. Instituto Superiore di Sanita, Rome, Italy **The subunit structure of bovine brain 14-3-2.** Brain Research (Amsterdam). 124(3):509-522, 1977.

Two aspects of the subunit structure of the bovine brain specific protein 14-3-2 were examined. Native 14-3-2 was separated into two fractions by hydroxylapatite chromatography. One eluted at the same position when chromatographed on the same column, while the other redistributed into the same two fractions again. Amino acid analysis of these two forms gave results that were not significantly different under the condition of analysis. Furthermore, when each peak was subjected to cyanogen bromide cleavage, very similar elution profiles of the resultant fragments were obtained. The two pools also cross-reacted with antiserum to 14-3-2. Reaction of purified 14-3-2 with dimethylsuberimidate caused the formation of covalently bound protein units of 100,000 molecular weight when measured by sodium dodecyl sulfate polyacrylamide gel electrophoresis, as opposed to the 50,000 minimal molecular weight normally detected. On the other hand, analysis of the soluble tryptic peptides of S-(14C)carboxymethyl 14-3-2 yielded only three distinct radioactive peptides, each with one residue of S-carboxymethylcysteine, whereas eight are expected on the basis of the amino acid composition of the 50,000 molecular weight polypeptide chains. The partial amino acid sequence of these peptides indicates that they represent four unique areas of the polypeptide chain. Since eight such peptides were expected, the minimum structural unit of the protein must be of 25,000 molecular weight, but may aggregate to form larger species. 23 references. (Author abstract)

003061 Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. Sheehan Inst. for Research, Inc., 767B Concord Ave., Cambridge, MA 02138 **A novel cannabinoid containing a 1,8-cineol moiety.** Experientia (Basel). 33(5):577-578, 1977.

The synthesis of a novel cannabinoid containing a 1,8,-cineol moiety is described. It is much less biologically active than delta1-tetrahydrocannabinol. 8 references. (Author abstract)

02 DRUG DEVELOPMENT (PRECLINICAL SCREENING)

003062 Ager, I. R.; Harrison, D. R.; Kennewell, P. D.; Taylor, J. B. Roussel Laboratories, Kingfisher Drive, Covingham, Swindon, Wiltshire, England **Synthesis and central nervous system activity of quinazolones related to 2-methyl 3-(o-tolyl) 4(3H)-quinazolone (methaqualone).** Journal of Medicinal Chemistry. 20(3):379-386, 1977.

A number of derivatives of 2-methyl-3-(o-tolyl)-4(3H)-quinazolone (methaqualone) bearing new substituents on the 2-methyl group were synthesized in an attempt to prepare improved hypnotics. CNS activities of the compounds were determined in the mouse using five methods: the loss of righting reflex, the rotating drum test, the antagonism of convulsions induced by maximal electroshock and pentylenetetrazole, and the antagonism of writhing induced by p-benzoquinone. It was established that most substitutions at the 2-methyl group position reduce or remove the CNS depressant activity of methaqualone. From the series prepared only the 2-fluoromethyl derivative or certain isothiouronium salts, which could be hydrolyzed in vivo to the 2-mercaptomethyl derivative, showed activity of the same magnitude as methaqualone. 28 references. (Author abstract modified)

003063 Fisher, M. H.; Grabowski, E. J. J.; Patchett, A. A.; ten Broeke, J.; Flataker, L. M.; Lotti, V. J.; Robinson, F. M. Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Rahway, NJ 07065 **5,11-Dimethyl 2,9-bis(phenylacetyl) 5,11 diazatetracyclo (6.2.2.0-2,7.0-4,9)dodecane, a potent, novel analgesic.** Journal of Medicinal Chemistry. 20(1):63-66, 1977.

The analgesic effects of 5,11-dimethyl-2,9-bis(phenylacetyl)-5,11-diazatetracyclo(6.2.2.0-2,7.04,9)dodecane (2a) were studied in mice and rats. All of the analgesic activity was attributable to the levorotatory isomer (2b) which was approximately three times as potent as morphine in the rat. Removal of one N-methyl group from 2a reduced, but did not abolish, the analgesic activity. The N-allyl analogues were neither agonists nor antagonists. Replacement of one of the phenyls of 2a with a cyclohexyl group yielded an analogue with considerable activity. Structural similarities with derivatives of ethenooripavine are noted. 15 references. (Author abstract modified)

003064 Gal, Joseph. School of Pharmacy, University of Wisconsin, Madison, WI 53706 **Stereochemistry of metabolism of amphetamines: use of (-) alpha-methoxy alpha(trifluoromethyl) phenylacetyl chloride for GLC resolution of chiral amines.** Journal of Pharmaceutical Sciences. 66(2):169-172, 1977.

Amphetamine and eight related compounds were reacted with a chiral acylating reagent to obtain, in each case, two diastereomeric amide derivatives. Gas layer chromatography conditions were found for the separation of the diastereomers in seven of the nine cases studied. Secondary amines were not derivatives under the reaction conditions used. A correlation between absolute configuration and elution order of the diastereomeric amides was observed for five compounds. The chiral acylating reagent was used in the determination of the enantiomeric composition of 2,5-dimethoxy-4-methylamphetamine excreted in rat urine after intraperitoneal drug administration. It is concluded that the chiral acylating reagent is suitable for the determination of the optical composition of compounds extracted from biological fluids. 26 references. (Author abstract modified)

003065 Hoffman, P. L.; Walter, Roderich; Bulat, M. Dept. of Physiology and Biophysics, University of Illinois at the Medical Center, Chicago, IL 60612 **An enzymatically stable peptide with activity in the central nervous system: its penetration through the blood-CSF barrier.** Brain Research (Amsterdam). 122(1):87-94, 1977.

The synthesis of a 14C labeled peptide, cyclo(Leu-Gly), is described, its stability to enzyme catalyzed inactiviation in vivo and in vitro is evaluated, and its rate of penetration through the blood cerebrospinal fluid (CSF) barrier in adult cats is determined. Only radioactivity was measured in plasma, CSF, and urine. Chromatography of ethanol extracts of each of the fluids revealed single spots corresponding to cyclo(Leu-Gly). Thus, the diketopiperazine was not metabolized to any detectable extent during the in vivo experiments, and all radioactivity represents the intact compound. Three hours after the injection of labeled cyclo(Leu-Gly), approximately 25% of the radioactivity was recovered in the urine; again, this represents intact compound. These experiments provide evidence that cyclo(Leu-Gly), which exhibits activity in the CNS when injected intravenously, rather easily penetrates the blood CSF barrier and remains as the intact peptide at a constant level in CSF and presumably brain for some time. 26 references. (Author abstract modified)

003066 Kirkpatrick, William E.; Okabe, Takayuki; Hillyard, Ira W.; Robins, Roland K.; Dren, Anthony T. ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, CA 92715 **3-Halo 5,7-dimethylpyrazolo (1,5-a) pyrimidines, a nonbenzodiazepinoid class of antianxiety agents devoid of potentiation of central nervous system depressant effects of ethanol or barbiturates.** Journal of Medicinal Chemistry. 20(3):386-393, 1977.

Forty derivatives of pyrazolo(1,5-a)pyrimidine, initially screened for antianxiety properties via gross behavioral observations in rats, were synthesized in order to explore possible structure activity relationships. Five of these compounds, including 5,7-dimethlpyrazolo(1,5-a)pyrimidine (6) and the 3-fluoro (7), 3-chloro (8), 3-bromo (9), and 3-iodo (10) derivatives, were selected for advanced evaluation. Although 6 and 7 had marginal activity, 8, 9, and 10 had an anxiolytic effect in animals comparable to the clinically useful benzodiazepines, diazepam, and chlorodiazepoxide. Comparison with chlorpromazine indicated that compounds 6 through 10 are probably not antipsychotic agents. These compounds also lacked activity in anticonvulsant and analgesic tests. Acute toxicity data (mouse, ip and po) indicated that 8, 9 and 10 had excellent therapeutic ratios, although 10 was more poorly absorbed than 8 and 9. Further demonstration of anxiolytic efficacy was obtained by comparing the effects of 8 and 9 with the benzodiazepines in modifying provoked aggression in monkeys, rats (muricide), and fighting mice. The most remarkable observation, however, was that 8 and 9 had no effect, at the anxiolytic threshold, in potentiating the CNS depressant effects of ethanol or sodium barbital (po) in treated mice. In contrast, diazepam and chlorodiazepoxide potentiated this drug interaction effect at minimal anxiolytic doses. 23 references. (Author abstract)

003067 Kohn, Harold; Kohn, Barbara A.; Steenberg, Marie Louise; Buckley, Joseph P. Department of Chemistry, University of Houston, Houston, TX 77004 **Syntheses and pharmacological activity of substituted imidazolidinethiones and thioimidazolines.** Journal of Medicinal Chemistry. 20(1):158-160, 1977.

A series of imidazolidinethiones and thioimidazolines was synthesized and tested for their effects on gross behavior in rats, on forced motor activity and spontaneous motor activity in mice, and for their ability to raise the threshold for convulsions induced by maximal electroshock, strychnine or pentylenetetrazole in mice. The thioimidazolines were the most active CNS depressants and had the highest safety index, while the isomeric imidazolidinethiones were much less effective and considerably more toxic. 11 references. (Author abstract modified)

003068 Lednicer, Daniel. Research Laboratories, Upjohn Company, Kalamazoo, MI 49001 **Butyrophenones from the isomeric 2-amino-5-phenylbicyclo(3.3.1)nonanes.** Journal of Medicinal Chemistry. 20(1):171-173, 1977.

The syntheses of the butyrophenone derivatives of 5-phenylbicyclo(3.3.1)nonyl-2-amine are described. The effects of the compounds on overt behavior and on nicotine toxicity in mice were determined. The present compounds were far less active than the corresponding cyclohexylamines as nicotine antagonists. 4 references.

003069 Matsumoto, Ken; Stark, Paul; Meister, Robert G. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206 **Cannabinoids. 1. 1-amino- and 1-mercapto 7,8,9,10-tetrahydro 6H dibenzo(b,d)pyrans.** Journal of Medicinal Chemistry. 20(1):17-24, 1977.

A series of 7,8,9,10-tetrahydro-6H-dibenzo(b,d)pyrans (THDP) was synthesized and evaluated in three rodent test systems (effects on hyperactivity in septal lesioned rats, effects on muricide by rats and effects on mouse exploratory behavior) for CNS activity. In general, a change of the 1-hydroxy group to an amine resulted in retention of pharmacological activity but a change to sulfur (mercapto group) resulted in loss of pharmacological activity. Derivatization of the 1-amino group with various functions decreased the activity of the compound. Optimum potency was obtained in all series with either a 1,1-dimethylheptyl or a 1,2-dimethylheptyl group in the 3 position. With either 1-hydroxy-THDP or 1-amino-THDP, preparation of the optically active antipodes produced compounds with a similar degree of pharmacological activity as measured in these rodent test systems. 21 references. (Author abstract modified)

003070 Pedersen, V.; Svendsen, O.; Danneskiold-Samsoe, P.; Boeck, V.; Moller, I. Dept. of Pharmacology and Toxicology, H. Lundbeck & Co., A. S. Ottilavej 7-9, DK-2500 Valby, Denmark **Pharmacology of cis(Z)-Clopenthixol decanoate, a depot neuroleptic.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(4):482-490, 1977.

The duration and intensity of the neuroleptic effect of cis(Z)-clopenthixol decanoate in Viscoleo are compared with those of dis(Z)-clopenthixol 2 HC1 in aqueous solution in a number of animal experimental models. Results indicated cis(Z)-clopenthixol 2HC1 had a strong, but short lasting neuroleptic effect (apomorphine antagonistic effect in dogs, inhibition of conditioned avoidance response in rats) which was accompanied by marked sedation. In contrast, cis(Z)-clopenthixol decanoate in oil had an effect which was slower in onset, but of much longer duration and only the highest doses caused a slight sedation. In rats catalepsy could be induced in some animals by high doses of cis(Z)-clopenthixol decanoate whereas cis(z)-clopenthixol 2 HC1 at all the doses tested caused catalepsy in all animals. In mice only high doses of cis(Z)-clopenthixol decanoate in oil caused reduction of spontaneous motor activity and potentiation of barbiturate anaesthesia. It was concluded that cis(Z)-clopenthixol decanoate in oil has a prolonged neuroleptic effect. Furthermore, the amount of active drug necessary to maintain a certain effect over a long period is considerably smaller with the depot preparation than with daily oral administration of cis(Z)-clopenthixol 2 HC1. 8 references. (Author abstract modified)

003071 Porsolt, R. D.; Le Pichon, M.; Jalfre, M. Departement de Neuropharmacologie, Synthelabo, SA, 58, rue de la Glaciere, F-75621 Paris Cedex 13, France **Depression: a new animal model sensitive to antidepressant treatments.** Nature (London). 266(5604):730-732, 1977.

A new behavioral animal model has been developed which both resembles depressive illness and is selectively sensitive to clinically effective antidepressant treatments. A rat, placed in a swimming tank from which there is no escape, eventually falls into a state of near immobility which is believed to reflect a state of lowered mood; this immobility can be reduced by such atypical antidepressants as iprindole, viloxazine, and mainserin. It is suggested that this method might be used to discover new types of antidepressant agents hitherto undetectable using classical screening tests. 15 references.

003072 Rice, Kenner C.; Klee, Werner A.; Aceto, Mario D.; Swain, Henry H.; Jacobson, Arthur E. National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, MD 20014 **Potential long acting opiate antagonists: preparation, pharmacological activity, and opiate-receptor binding of N-substituted 2'-hydroxy 5-methyl-9alpha-propyl 6,7-benzomorphans.** Journal of Pharmaceutical Sciences. 66(2):193-197, 1977.

A homologous series of N-substituted 2'-hydroxy-5-methyl-9alpha-propyl-6,7-benzomorphans was prepared and their pharmacological activity studied in monkeys. The N-pentyl and N-hexyl derivatives did not have the analgesic potency of the parent N-methyl compound. They were found to be narcotic antagonists with a long duration of action. All of the N-substituted 9alpha-propylbenzomorphans, except for methyl, heptyl, and octyl, had antagonist activity. The receptor binding constants of the N-alkyl compounds were found to be uniformly twofold to threefold lower than those of the N-substituted normetazocines. 26 references. (Author abstract modified)

003073 Sugiura, Shoji; Ohno, Sachio; Ohtani, Osamu; Izumi, Kihachiro; Kitamikado, Tadashi; Asai, Hajime; Kato, Kazuo; Hori, Mikio; Fujimura, Hajime. Research Laboratories, Maruko Seiyaku Company Ltd., Teramae-1212, Gejo-cho, Kasugai 486, Japan **Syntheses and antiinflammatory and hypnotic activity of 5-alkoxy 3 (N-substituted carbamoyl) 1-phenylpyrazoles.** Journal of Medicinal Chemistry. 20(1):80-85, 1977.

The syntheses of 5-alkoxypyrazoles which have the N substituted carbamoyl group in the 3 position on the pyrazole ring are described. Four of the compounds showed antiinflammatory activity and three possessed hypnotic properties when tested in rats and in mice. 5 references. (Author abstract modified)

003074 Taberner, Peter V.; Pearce, Martin J.; Watkins, Jeffrey C. Department of Pharmacology Medical School, University of Bristol, Bristol 8, England **The inhibition of mouse brain glutamate decarboxylase by some structural analogues of L-glutamic acid.** Biochemical Pharmacology. 26(4):345-349, 1977.

A series of amino acid hydroxamates and mercapto carboxylic acids were tested in order to discover inhibitors of mouse brain glutamate decarboxylase (GAD) and GABA-aminotransferase (GABA-T) and to determine whether or not compounds having some affinity for other sites of glutamate binding can inhibit GAD. Malate, thiomalate, glutarate and L-glutamic acid gamma-hydroxamate were potent competitive inhibitors of GAD with respect to glutamate, and were far less active against GABA-T. None of these compounds reacted directly with free pyridoxal phosphate. Other compounds, including cysteamine, dl-methionine hydroxamate, D-penicillamine and dl-cysteine inhibited both enzymes and formed stable complexes with free pyridoxal phosphate. Possible structural requirements for the competitive binding of an inhibitor to the active site of GAD are discussed. 20 references. (Author abstract modified)

003075 Welch, Willard M.; Harbert, Charles A.; Sarges, Reinhard; Stratten, Wilford P.; Weissman, Albert. Pfizer Inc., Medical Research Laboratories, Groton, CT 06340 **Analgesic and tranquilizing activity of 5,8-disubstituted 1-tetralone Mannich bases.** Journal of Medicinal Chemistry. 20(5):699-705, 1977.

Synthesis and pharmacological evaluation were made of a number of 1-tetralone Mannich bases to test whether 5,8-disubstituted analogs might possess more potent neuroleptic activity than the unsubstituted derivatives previously reported. 5,8-Disubstituted 1-tetralone Mannich bases represent semirigid variants of classical (i.e.,chlorpromazine) neuroleptic agents. 8-Chloro-5-methoxy-2-morpholinomethyl-1-tetralone exhibits neuroleptic potency in the thiothixene range in animal models. Of greater potential interest, however, is the analgesic potency of the 8-chloro-5-methoxy-2-pyrrolidinomethyl analogue which was in the morphine range. This compound did not induce tolerance nor was its activity reversed by naloxone. The series displayed high dependence of analgesic activity on the type of aromatic substitution. Ring size and relative positions of the aryl ring and amino nitrogen are critical to activity. 18 references. (Author abstract modified)

003076 Wiberg, Asa; Wahlstrom, Goran; Oreland, Lars. Department of Pharmacology, University of Umea, S-90187 Umea, Sweden **Brain monoamine oxidase activity after chronic ethanol treatment of rats.** Psychopharmacology (Berlin). 52(2):111-113, 1977.

The effects of chronic ethanol treatment on brain monoamine oxidase were studied in rats. Rats were given chronic treatments with ethanol in two ways: by offering 10% ethanol in water as the only liquid supply for 34 weeks and by exposing the rats to ethanol vapor during 5 h daily for 7 weeks. In this way blood ethanol levels of 1.4-2.3and 5.5-6.9mg/ml, respectively, were accomplished. In neither of the cases was brain monoamine oxidase activity changed. The result supports a hypothesis previously advanced that the lowered monoamine oxidase activity found in the brain of a suicide patient was not due to a direct effect of ethanol on alcoholics in the suicide group, but that the low enzyme activity reflected a low monoaminergic activity in the brains of the patients in the suicide group. 14 references. (Author abstract modified)

03 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

003077 Aceto, M. D.; Flora, R. E.; Harris, L. S. Medical College of Virginia, Department of Pharmacology, Virginia Commonwealth University, Richmond, VA **The effects of naloxone and nalorphine during the development of morphine dependence in rhesus monkeys.** Pharmacology (Basel). 15(1):1-9, 1977.

The effects of two narcotic antagonists naloxone and nalorphine, during the development of morphine dependence in 47 rhesus monkeys in a randomized, blind experiment were studied. Monkeys were habituated to 3mg morphine/kg every 6 hr. At 30, 60, and 90 days, monkeys were given .025mg to .2mg naloxone/kg, .25mg to 2mg nalorphine/kg, or saline.

Animals were then scored for withdrawal symptoms. The results suggest that: 1) significant dose related differences exist for combined number of withdrawal symptoms times frequency of occurrence; 2) naloxone and nalorphine are qualitatively similar; 3) antagonists are more effective as dependency develops; 4) naloxone is approximately 10 times as potent as nalorphine; and 5) vomiting was the only withdrawal sign for which ED50 could be calculated. Dependence on morphine appeared to increase up to 9 months after the 90 day stabilization period. 5 references.

003078 Aghajanian, G. K.; Bunney, B. S. Yale University School of Medicine, 34 Park St., New Haven, CO 06508 **Dopamine "autoreceptors": pharmacological characterization by microiontophoretic single cell recording studies.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(1):1-7, 1977.

The effects on the firing of single dopamine (DA) neurons in the substantia nigra and adjacent ventral tegmental area of a representative group of catacholamine agonists and antagonists were studied in rats using single cell recording and microiontophoretic techniques. Microiontophoretic application of DA or the DA agonist apomorphine depressed the firing of these cells; the DA antagonist trifluoperazine blocked the effect. However, the alpha agonist clonidine had no depressant effect and the beta agonist isoproteronol had only a weak depressant action on DA neurons. Furthermore, the alpha antagonist piperoxane and the beta antagonist sotolol were completely ineffective in blocking the depressant effects of DA. The results indicate that DA sensitive receptors on the soma of DA neurons are pharmacologically distinct from alpha or beta-adrenoreceptors. Because of their location and selective responsiveness to DA agonists, the catecholamine receptors on the soma of DA neurons appear best classified as DA "autoreceptors". 36 references. (Author abstract modified)

003079 Ahlenius, Sven; Engel, Jorgen. Department of Pharmacology, University of Goteborg, Fack, S-400 33 Goteborg 33, Sweden **Potentiation by a-methyltyrosine of the suppression of food-reinforced lever-pressing behaviour induced by antipsychotic drugs.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(1):115-125, 1977.

The mode of action by which alpha-methyltyrosine (alpha-MT) potentiates the suppression of food reinforced, lever pressing behavior induced by catecholamine receptor blocking, antipsychotic drugs was investigated in rats trained to lever press for food on a fixed-ratio schedule of reinforcement. Alpha-MT potentiated the effects induced by pimozide, which preferentially blocks central dopamine (DA) receptors, but not those induced by phenoxybenzamine, which blocks central noradrenaline (NA) receptors. The behavioral suppression induced by chlorpromazine, thioridazine, or haloperidol were not potentiated by the DA-beta-hydroxylase inhibitor bis-(4-methyl-1-homopiperazinylthiocarbonyl) disulfide (FLA-63). It is suggested that: 1) alpha-MT potentiates the actions of antipsychotic drugs by blocking a feedback mediated compensatory increase in catecholamine synthesis resulting from a blockade of central NA receptors and/or DA receptors; 2) the disruption of conditioned behaviors by antipsychotic drugs is probably due to a blockade of central DA receptors; and 3) a blockade of DA neurotransmission is of primary importance for the clinical effects induced by antipsychotic drugs. 30 references. (Author abstract modified)

003080 Akerman, Karl E.; Jarvisalo, Jorma O. Dept. of Medical Chemistry, University of Helsinki, Siltavourenpenger 10, SF-00170 Helsinki 17, Finland **Effect of propranolol and related drugs on transmembraneous pH differences in liposomes.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(4):497-504, 1977.

The effect of propranolol and related drugs on pH gradients and inophore mediated ion exchange fluxes over liposomal membranes was studied. Liposomes were prepared by the method of saha et. al.,either in a medium containing 60mM choline chloride or 80mM KCl. When the external pH was neutral and the internum of the liposomes acidic, the drug decreased the pH gradient. When the externum was acidic and the internum neutral, the gradient was increased by the drug. The effect of butacaine was similar to that of propranolol, while procaine, timolol and practolol were ineffective. It is suggested that the charged form of propranolol is bound to the membrane and dislocates protons from binding sites in the membrane. After penetration it could associate with protons in the intraliposomal compartment and hence increase the pH of the interior. Depending on the direction of the preexisting proton gradient propranolol would thus be able to increase or decrease the pH difference across the lipsomal membrane. 18 references. (Author abstract modified)

003081 Amit, Z.; Levitan, Deborah E.; Brown, Z. W.; Rogan, F. Department of Psychology, Sir George Williams Campus, Concordia University, Montreal, Quebec, Canada **Possible involvement of central factors in the mediation of conditioned taste aversion.** Neuropharmacology (Oxford). 16(2):121-124, 1977.

The possible involvement of central mechanisms in the mediation of cannabis induced conditioned taste aversion was studied in rats. Intraperitoneal injections of delta9-tetrahydrocannabinol, (delta9-THC), morphine, and ethanol all produced conditioned taste aversions. However, at the doses used, none of the drugs produced conditioned taste aversions after infusion into the caudate nucleus, and only delta9-THC produced a taste aversion after infusion into the dorsal hippocampus. The data are discussed in terms of a possible specific interaction between delta9-THC and the dorsal hippocampus in the central induction of a conditioned taste aversion. 20 references. (Author abstract modified)

003082 Anderson, Stuart D.; Basbaum, Allan I.; Fields, Howard L. Dept. of Neurology, University of California, San Francisco, CA 94143 **Response of medullary raphe neurons to peripheral stimulation and to systemic opiates.** Brain Research (Amsterdam). 123(2):363-368, 1977.

The responses of medullary raphe neurons to peripheral stimulation and to morphine and nalozone were studied in cats. A large proportion of neurons within and adjacent to the medullary raphe were found to have somatosensory receptive fields. The majority of these neurons responded to innocuous stimuli, but about half responded maximally to stimuli of noxious intensity. The ongoing activity of 12 ventromedial medullary cells was excited by intravenous (IV) morphine and inhibited by IV naloxone in every instance in which concomitant blood pressure changes were not produced. The findings support the hypothesis that morphine induced analgesia is mediated (at least partially) by activation of nucleus raphe magnum (NRM) neurons which then inhibit spinal pain transmission neurons. 19 references.

003083 Aranda, G.; Vuillaume, M. Ecole Polytechnique, Laboratoire de Synthese Organique F-91120 Palaiseau, France **/Metabolism of fluorinated mescalins by Pieris brassicae (Insect, Lepidoptera)./** Etude du metabolisme de mescalines fluorees

par Pieris Brassicae (insecte, Lepidoptere). Experientia (Basel). 33(2):261-262, 1977.

The metabolic action of alpha-fluorinated mescaline on induction of diapause in the cabbage butterfly (Pieris brassicae) was studied. The introduction of fluorine into mescaline has no influence on this activity. This result suggests solvolysis of fluorine and in vivo formation of a common ethylenimine intermediate. Activity decreases, however, with substitution of nitrogen. 11 references. (Author abstract modified)

003084 Aronson, Carl E.; Serlick, Elaine R. Laboratories of Pharmacology, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA 19174 **Effects of chlorpromazine on the isolated perfused rat heart.** Toxicology and Applied Pharmacology. 39(2):157-176, 1977.

Studies performed to determine the simultaneous effects of chlorpromazine on metabolic, mechanical, and electrical activity in the isolated perfused rat heart at concentrations comparable to those employed in human and animal subjects are presented. Perfusion of hearts with chlorpromazine HC1(50-5000ng/ml) caused significant changes in heartrate, coronary flow, isometric systolic tension, certain metabolite concentrations, and electrical activity. Phosphorylase alpha activity remained normal. Chlorpromazine (50ng/ml) decreased isometric systolic tension and prolonged QT interval in the elctrocardiogram. Fructose 1,6diphosphate and pyruvate concentrations were elevated, suggesting aldolase inhibition and decreased pyruvate utilization. Similar results were obtained at 500ng/ml. At 5000ng/ml, heart rate and isometric systolic tension were markedly diminished. Coronary flow increased briefly but returned to normal. PR, QTalpha and QT intervals were prolonged. Fructose 1,6-diphosphate, glyceraldehyde3phosphate, and pyruvate concentrations in the tissue increased, while the amount of dihydroxyacetone phosphate and L-(-)glycerol-l-phosphate decreased. No chlorpromazine induced lesions, gross or microscopic, were found. 30 references. (Author abstract modified)

003085 Arora, Ramesh C.; Meltzer, Herbert Y. Department of Psychiatry, University of Chicago Pritzker School of Medicine, Chicago, IL 60637 **Characterization of rat skeletal muscle monoamine oxidase.** Biochemical Pharmacology (Oxford). 26(1):45-49, 1977.

Optimal conditions for deamination of 5-hydroxytryptamine in rat skeletal muscle were determined. The presence of monoamine oxidase (MAO) A and MAO B isozymes was demonstrated by the use of tyramine, specific substrates (serotonin and benzylamine), and specific inhibitors (clorgyline and deprenyl) of MAO A and B respectively. A 6.5:3.5ratio of MAO A to B was found using a whole muscle homogenate, while a 7.5:2.5ration was found with isolated mitrochondria. Thermal inactivation studies demonstrated that skeletal muscle MAO A is more susceptible to heat inactivation than MAO B. The approximate proportion of muscle homogenate MAO which is present in sympathetic nerves was found to be 18%, as determined by treating rats with 6-hydroxydopamine and quantifying the decrease in activity. Significant inhibition of MAO activity was observed after administration in vivo of the MAO inhibitors pargyline, tranylcypromine and harmaline. 28 references. (Author abstract)

003086 Ary, Marylouise; Cox, Barry; Lomax, Peter. Department of Pharmacology, UCLA School of Medicine and the Brain Research Institute, Los Angeles, CA 90024 **Dopaminergic mechanisms in precipitated withdrawal in morphine-dependent rats.** Journal of Pharmacology and Experimental Therapeutics. 200(2):271-276, 1977.

The role of dopamine in morphine withdrawal precipitated by naloxone injection was determined by pretreating morphine dependent male rats with apomorphine or pimozide. Withdrawal was assessed by scoring each of the following signs individually: chewing, licking, teeth chattering, facial tremor, grooming, writhing, diarrhea, weight loss, wet dog shakes, head shakes and hypothermia. Apomorphine in the lower dose range (0.625-1.25mg/kg) produced a significant decrease in teeth chattering, writhing, weight loss, and wet dog shakes. The high dose of apomorphine (2.5mg/kg) significantly inhibited all features of the withdrawal except writhing and weight loss. Pimozide caused a significant increase in chewing, writhing, and head shakes, but only with the highest dose used (0.5mg/kg). Pimozide (0.5mg/kg) significantly reduced withdrawal hypothermia, but apomorphine had no effect on this sign except at the highest dose when withdrawal hypothermia was increased. The results suggest that some of the withdrawal signs may involve a dopaminergic mechanism, but the expression of these signs may be due to an increase or a decrease in dopaminergic activity, depending on the sign studied. This suggests the need to be specific about which signs are being used to assess dependence when discussing the involvement of putative neurotransmitters on the withdrawal phenomenon. 28 references. (Author abstract modified)

003087 Atrens, D. M.; Ungerstedt, U.; Ljungberg, T. Dept. of Psychology, University of Sydney, Sydney, 2006, N.S.W., Australia **Specific inhibition of hypothalamic self-stimulation by selective reuptake blockade of either 5-hydroxytryptamine or noradrenaline.** Psychopharmacology (Berlin). 52(2):177-180, 1977.

The effects of two new phthalane derived bicyclic thymoleptics, LU-10-171 and LU-5-003, which are potent and highly selective reuptake blockers of 5-hydroxytryptamine (5-HT) and noradrenaline (NA), respectively, on hypothalamic stimulation were studied in rats. The use of a two-way shuttlebox permitted the differentiation of specific reward modulation effects from the variety of nonspecific performance changes that these drugs may produce. Selective reuptake blockade of either 5-HT or NA produced a dose dependent reduction in reward that could be clearly dissociated from any nonspecific performance decrements. Besides providing direct evidence for a significant role for 5-HT in the mediation of hypothalamic self-stimulation, these data show that simply increasing transmitter availability is not a sufficient condition to enhance self-stimulation reward. It is suggested that self-stimulation is dependent on response contingent transmitter release and that any operation that increases reward transmitter availability in a response independent manner should attenuate self-stimulation. 20 references. (Author abstract modified)

003088 Atweh, Samir F.; Kuhar, Michael J. Department of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **Autoradiographic localization of opiate receptors in rat brain. I. spinal cord and lower medulla.** Brain Research (Amsterdam). 124(1):53-67, 1977.

Male rats (N=15) were injected with tritiated diprenorphine (an opiate antagonist) or tritiated etorphine (an opiate agonist) to autoradiographically investigate localization of opiate receptors in the spinal cord and lower medulla. With diprenorphine, the opiate receptors were highly localized to: 1) layers I (marginal cell zone) and II (substantia gelatinosa) of the dorsal horn of the spinal cord; 2) the substantia gelatinosa of the spinal trigeminal nucleus; 3) components of the vagal system, including the vagus nerve, nucleus tractus solitarius, nucleus commissuralis, nucleus intercalatus, nucleus ambiguus and

nucleus originis dorsalis vagus; and 4) the area postrema. Examination of etorphine binding sites showed the same distribution. It is concluded that, in these brain regions, opiate receptors are highly associated with areas receiving small, afferent primary fibers, and are strategically placed to modulate noxious stimuli as well as explain some visceral side-effects of opiate administration. 70 references. (Author abstract modified)

003089 Audigier, Y.; Malfroy-Camine, B.; Schwartz, J. C. Unite 109 de Neurobiologie, Centre Paul Broca de l'INSERM, 2ter rue d'Alesia, F-75014 Paris, France **Binding of 3H-leu-enkephalin in rat striatum: partial inhibition by morphine or naloxone.** European Journal of Pharmacology (Amsterdam). 41(2):247-248, 1977.

The inhibition of 3H-leu-enkephalin binding by morphine or naloxone was studied at two concentrations (5 and 25nM) of the peptide selected. Data indicated that naloxone and morphine inhibit similarly, in a concentration related manner, a fraction of the 3H-leu-enkephalin binding. Moreover, the maximal inhibition was found to be the same at 5 or 25nM 3H-leu-enkephalin. 3 references.

003090 Baldeo, Wilfred; Gilbert, John N. T.; Powell, John W.; Jones, Lyndon V.; Whitehouse, Michael J. School of Pharmacy, 29/39 Brunswick Square, London, WC1N 1AX, England **A new metabolite of amylobarbitone: 5-(3'-carboxybutyl)-5-ethylbarbituric acid.** Journal of Pharmacy and Pharmacology (London). 29(4):254, 1977.

The identification of 5-(3'-carboxy-butyl)-5-ethylbarbituric acid as an additional urinary metabolite of amylobarbitone, based on an analysis of the urine samples of a male volunteer, forensic urine samples, and an amylobarbitone overdose case, is reported. Synthesis of this metabolite necessary to its final confirmation and quantification has been begun. 4 references.

003091 Baumgold, J.; Abood, L. G.; Aronstam, R. Laboratory of Neurobiology, National Institute for Mental Health, Bethesda, MD 20014 **Studies on the relationship of binding affinity to psychoactive and anticholinergic potency of a group of psychotomimetic glycolates.** Brain Research (Amsterdam). 124(2):331-340, 1977.

A study of the possible relationship of the binding affinity of a series of anticholinergic psychotomimetic drugs to their psychopharmacological and anticholinergic effects is reported. Binding was measured to brain homogenates and nerve endings using 3H quinuclidinyl benzilate (QB), a psychotomimetic agent presumable affecting muscarinic sites in the brain. The two stereoisomers of QB were compared; although the L-isomer had 15 times the binding affinity of D-isomer, the L-isomer had over 200 times the psychopharmacologicalpotency of the D-form. When the relative binding affinity of a homologous series of glycolate esters was compared with their relative psychoactive potency, the correlation was excellent; however, when compounds with heterocyclic amino rings other than quinuclidine and piperidine were considered, the correlation was poor. The correlation between binding affinity and antagonism to acetylcholine induced onctraction of ileum was more consistent. A study on the effect of added lipids on QB binding to nerve endings is also included and it found that phosphatidyl serine had a significant enhancing effect while gangliosides were inhibitory. Results established that exogenous lipids, particularly phosphatidyl serine, significantly enhance QB binding to brain tissue. 24 references. (Author abstract modified)

003092 Beaubien, A. R.; Mathieu, L. F.; Huddleston, J. A.; James H. F. Drug Toxicology Division, Health Protection Branch, Department of National Health and Welfare, Ottawa, Ontario, Canada **Subacute imipramine: changes in single dose pharmacokinetics in rats.** Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 225(1):6-16, 1977.

Because tricyclic antidepressants are typically administered for several weeks or months to depressed patients, the pharmacokinetics of 14C imipramine (14C IP) were examined after a 3 week period of oral imipramine (IP) administration in male Wistar rats. IP administered twice daily for 3 weeks more than halved the control rate of body weight gain. A bile fistula was inserted after this period and 14C IP was administered 14-18 hr after the final scheduled dose. Biliary excretion of radioactivity during the subsequent 50 min was decreased to 60% of control. Higher levels of gastrointestinal radioactivity (mainly in the stomach lumen) indicated a slower imipramine absorption rate in the subacute group. Liver metabolite ratios revealed that the treatment group had decreased rates of 2-hydroxylation and 10-hydroxylation, but not demethylation, of imipramine. After incubation of the 25-50 min bile sample with glusulase, bile to liver ratios of metabolites indicated a lower entry rate of imipramine, desmethylimipramine and 2-hydroxydesmethylimipramine, but not of 2-hydroximipramine or 10-hydroximipramine, into the bile of the subacute imipramine group. 17 references. (Author abstract)

003093 Bell, James A.; Martin, William R. National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, KY **The effect of the narcotic antagonists naloxone, naltrexone and nalorphine on spinal cord C-fiber reflexes evoked by electrical stimulation or radiant heat.** European Journal of Pharmacology (Amsterdam). 42(2):147-154, 1977.

The effect of the narcotic antagonists naloxone (NX), naltrexone (NTX), and nalorphine (NP) on cat spinal cord C-fiber reflexes evoked by electrical stimulation or radiant heat was studied. The reflexes were recorded from an S1 ventral root in the acute decerebrate low spinal cat following stimulation of the ipsilateral superficial peroneal nerve or application of radiant heat to the metacarpel footpad. NX and NT increased the electrically evoked C-fiber reflex and NX increased the radiant heat evoked ventral root reflex in doses too small to have nonspecific excitatory effects; NT was not tested in the radiant heat experiment. NP facilitated the electrically evoked C-fiber reflex at a dose level that was depressant to the flexor reflex in the chronic spinal dog. WIN-35,197-2 and morphine depressed both the C-fiber and radiant heat evoked reflexes indicating that both mu and kappa receptors are present in the cat spinal cord. NX was more effective in antagonizing the depressant effects of morphine than those of WIN-35,197-2. The results support the hypothesis that a naturally occurring opiate-like agonist which exerts inhibitory modulation of the C-fiber reflex of the cat is mu type since very low doses of NX and NTX produce facilitatory effects. 31 references.

003094 Berger, Denis; Weiner, Henry. Department of Biochemistry, Purdue University, West Lafayette, IN 47907 **Effects of disulfiram and chloral hydrate on the metabolism of catecholamines in rat liver and brain.** Biochemical Pharmacology (Oxford). 26(8):741-747, 1977.

The effects of disulfiram and chloral hydrate on the metabolism of catecholamines were investigated in rat liver and brain by measuring distribution of catabolites obtained from catecholamines after inhibition of aldehyde dehydrogenase (ALDH). Incubations of tissues and perfusions

of the caudate nucleus of conscious animals were performed with carbon labeled catecholamines. Data from slice incubations showed that disulfiram inhibited brain ALDH more effectively than the liver enzyme, as measured by the decreased formation of 3,4-dihydroxyphenylacetic acid, and disulfiram increased the rate of deamination of dopamine in liver slices but did not alter the rate of dopamine deamination in brain tissues. Tetrahydropapaveroline was formed in experiments utilizing dopamine, with some deaminated dopamine recovered as the alkaloid. A nonidentified metabolite of dopamine was isolated, primarily from brain tissues. Chloral hydrate did not significantly affect the metabolism of dopamine in either organ, and metabolism of noradrenaline was not significantly altered by either drug. Data from the brain perfusions confirmed conclusions from incubations of slices: disulfiram is a potent inhibitor of 3,4-dihydroxyphenylacetic acid formation, while chloral hydrate is virtually ineffective at inhibiting the acid formation. 27 references. (Author abstract modified)

003095 Bevan, P.; Bradshaw, C. M.; Szabadi, E. Department of Psychiatry, University of Manchester, The Medical School, Oxford Road, Manchester M13 9PT, England **The effect of desipramine on the uptake of mescaline by cortical synaptosomes.** Biochemical Pharmacology (Oxford). 26(3):207-210, 1977.

The effect of desipramine on the uptake of radiolabeled noradrenaline (NA) and mescaline into a synaptosome rich preparation from the rat cerebral cortex was studied. NA was accumulated by the tissue by a temperature dependent process which was competitively inhibited by desipramine. Mescaline was accumulated by a temperature dependent and sodium dependent process which was not affected by desipramine. The uptake of NA was inhibited by mescaline in a noncompetitive manner. It is suggested that the uptake of mescaline is not brought about by the NA uptake mechanism. 16 references. (Author abstract modified)

003096 Biggio, G.; Costa, E.; Guidotti, A. no address **Pharmacologically induced changes in the 3':5'-cyclic guanosine monophosphate content of rat cerebellar cortex: difference between apomorphine, haloperidol and harmaline.** Journal of Pharmacology and Experimental Therapeutics. 200(1):207-215, 1977.

A study was conducted in rats to pharmacologically characterized the different mechanisms by which apomorphine, harmaline and isoniazid increase the cyclic 3',5'-guanosine monophosphate (cGMP) content of cerebellar cortex. Harmaline increased cerebellar cGMP content in a dose related manner; this increase was prevented by pretreatment with 3-acetylpyridine (3-AP), which destroys climbing fibers and inhibits harmaline induced tremor. Isoniazid produced increases in cGMP content which were not affected by pretreatment with 3-AP. Since isoniazid decreases cerebellar gamma-aminobutyric acid (GABA) levels, the increase in cGMP might reflect a reduction in the availability of GABA at the level of postsynaptic receptors. Apomorphine increased cGMP content of cerebellar cortex; haloperidol decreased it. These effects were not altered by 3-AP. It is suggested that the cGMP content of cerebellar cortex fluctuates in response to changes in the afferent stimulatory input to the cerebellum, increasing when the activity of either climbing fibers of mossy fibers is increased and decreasing when either of these two stimulatory inputs is reduced. 41 references. (Author abstract modified)

003097 Biggio, G.; Guidotti, A. Department of Pharmacology, University of Cagliari, Medical School, Cagliari, Italy **Regulation of cyclic GMP in cerebellum by a striatal dopaminergic mechanism.** Nature (London). No. 5591:240-242, 1977.

Changes in cerebellar cyclic 3',5'-guanosine monophosphate (cyclic GMP) content in rats elicited by intrastriatal, intracerebellar, and intraperitoneal injection of different neuroleptics and apomorphine were compared. The intraperitoneal injection of haloperidol, chloropromazine, and (+)-butaclamol produced a dose related decrease of the cyclic GMP content of cerebellar cortex. Results show that (-)-butaclamol failed to decrease the cerebellar content of cyclic GMP. Haloperidol and (+)-butaclamol also decreased the content of cyclic GMP in cerebellar cortex when they were directly infused into the striatum. Cerebellar cortex cyclic GMP was reduced by intrastriatal injection of haloperidol or (+)-butaclamol; no change was seen, however, when the drugs were directly applied to the cerebellum, and (-)-butaclamol did not change cerebellar cyclic GMP content after either intrastriatal or intracerebellar injection. It is concluded that the results support the idea that the functional state of striatal dopamine receptors may be responsible for changes of cerebellar cyclic GMP. A study of the action of apomorphine injected intrastriatally on the cyclic GMP content of cerebellar cortex demonstrates that the content of cerebellar cyclic GMP can be influenced by activating dopamine receptors in basal ganglia. Measurement of cerebellar cyclic GMP may possibly be a sensitive biochemical index of the impairment of striatal function elicited by antipsychotics: the results may also be interpreted as preliminary evidence for a cerebellar role in some of the actions of neuroleptic drugs. 17 references.

003098 Bird, Stephanie J.; Kuhar, Michael J. Department of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **Iontophoretic application of opiates to the locus coeruleus.** Brain Research (Amsterdam). 122(3):523-533, 1977.

Male albino rats (N=25) were administered opiates iontophoretically to investigate: 1) the effects of the drugs on the spontaneous activity of single neurons in and around the locus coeruleus; 2) the anatomical distribution of neurons responsive to morphine compared with autoradiographically determined distribution of opiate receptors; and 3) the pharmacological characteristics of observed opiate sensitivity. The vast majority of morphine sensitive single units in the area examined were localized to the locus coeruleus. This corresponded well with the known distribution of the highest densities of opiate receptor sites in this region of the midbrain. Morphine produced a marked and prolonged depression of spontaneous activity. Levorphanol produced an effect similar to that of morphine while comparable doses of dextrorphan, the clinically inactive stereoisomer, did not. Naloxone and levallorphan prevented, as well as reversed, the depression due to application of agonists. While the units were depressed following the application of opiate agonists, the cells were still excited by the neurotransmitter acetylcholine. It is concluded that neuronal sensitivity to opiates has a high positive correlation with autoradiographically determined opiate receptor sites, and that this sensitivity to opiates is blocked by opiate antagonists and is stereospecific in nature. 53 references. (Author abstract modified)

003099 Bloom, Alan S.; Dewey, William L.; Harris, Louis S.; Brosius, Keith K. Dept. of Pharmacology, Medical College of Wisconsin, Milwaukee, WI 53201 **9-nor-9beta-hydroxyhexahydrocannabinol, a cannabinoid with potent antinociceptive activity: comparisons with morphine.** Journal of Pharmacology and Experimental Therapeutics. 200(2):263-270, 1977.

The antinociceptive activities of (plus/minus)9-nor-9beta-hydroxyhexahydrocannabinol effects of beta-HHC on the accumulation of newly synthesized dopamine (DA) and norepinephrine (NE) in the brains of untreated, naloxone pretreated and morphine tolerant male albino mice were studied in order to determine whether the mechanism of action of beta-HHC was similar to that of morphine. Beta-HHC was about equipotent with morphine in the tail flick test. The alpha-isomer of beta-HHC and delta9-tetrahydrocannabinol were much less active than beta-HHC. The cannabinoids did not significantly affect the endogenous levels of DA and NE or the precursor pools, but beta-HHC produced dose dependent increases in the accumulation of newly synthesized DA and NE. Pretreatment with naloxone antagonized both the tail flick activity and blocked the increases in catecholamine synthesis produced by beta-HHC. Cross-tolerance between beta-HHC and morphine did not exist in regard to either tail flick activity or increased catecholamine synthesis. The results suggest that beta-HHC may share some properties with the narcotic analgesics but that significant differences exist, and provide further evidence that catecholamine containing neurons are involved in the central mediation of the tail flick response. 36 references. (Author abstract modified)

003100 Blum, K.; Futterman, S.; Wallace, J. E.; Schwertner, H. A. Department of Pharmacology, University of Texas Health Science Center, San Antonio, TX 78284 **Naloxone-induced inhibition of ethanol dependence in mice.** Nature (London). No. 5589:49-51, 1977.

To test the antagonistic properties of naloxone toward ethanol, physical dependence on ethanol was induced in 24 male Swiss-Webster mice. The animals then received either naloxone or equivalent volumes of saline every 6 hours for 4 days. It was found that the injections of naloxone significantly inhibited convulsions in response to ethanol withdrawal. This reaction was found to be consistent in three further experiments using a total of 72 mice. It is emphasized that these results, showing antagonism by naloxone of nonopiate drugs, must be viewed with caution inasmuch as it is possible that naloxone, though considered to be a specific opiate receptor antagonist, has other actions so far unappreciated. The results would then simply reflect the action of naloxone at the alternative site(s) of action, and would support the interpretation that ethanol and the opiates share some common biochemical mechanisms. 21 references.

003101 Bodzenta, Anna; Wisniewski, Konstanty. Department of Pharmacology, Institute of Physiology and Biochemistry, Medical School, Bialystok, Poland **The effect of prostaglandin E1 on central cholinergic mechanisms.** Pharmacology (Basel). 15(2):143-151, 1977.

The influence of prostaglandin E1 (PGE1) and its precursor diholo-gamma-linolenic acid on the central action of acetylcholine was studied in animals. PGE1 and dihomo-gamma-linolenic acid increased the depressive action of acetylcholine as evaluated with Lat's and thiopental sleeping time tests. PGE1 and its precursor diminished or eliminated the influence of acetylcholine on pentetrazol convulsion. Endogenous acetylcholine in excess inhibited hyperthermic effect of PGE1. The results show that PGE1 and its precursor may change the action of acetylcholine in the central nervous system. 27 references. (Author abstract)

003102 Boggan, William O.; Meyer, Jerrold S. Department of Psychiatry, Medical University of South Carolina, Charleston, SC 29401 **Effects of serotonergic drugs on methaqualone-induced hypothermia.** Research Communications in Chemical Pathology and Pharmacology. 16(4):629-636, 1977.

The hypothesis is tested that the biogenic amine serotonin plays a role in the hypothermic action of methaqualone, a nonbarbiturate sedative hypnotic. Methaqualone (75mg/kg) produced a significant decrease in the rectal temperature of mice. This effect was antagonized by parachlorophenylalanine and potentiated by Lilly 110140. These compounds also decreased and increased respectively the circulating concentration of methaqualone. 23 references. (Author abstract modified)

003103 Borri-Voltattorni, C.; Minelli, A.; Borri, P. Institute of Nervous and Mental Diseases, University of Perugia, Perugia, Italy **Interaction of N-(DL-seryl)N-(2,3,4-trihydroxybenzyl)-hydrazine with L-Dopa decarboxylase from pig kidney.** Experientia (Basel). 33(2):158-160, 1977.

Interaction of seryltrihydroxybenzylhydrazine (Ro 4-4602) with a highly purified preparation of dopadecarboxylase from pig kidney was studied. This compound which does not pass the blood-brain barrier at therapeutic doses was found not to be a powerful inhibitor in vitro. Kinetic and spectral data suggest some possibilities on the binding nature of the inhibitor and substrates. 10 references. (Author abstract)

003104 Bosse, A. Abt. Biochemische Pharmakologie, Max Planck Institut fur experimentelle Medizin, Hermann Rein Str. 3, D-34 Gottingen, Germany **In vitro studies in synaptosomes of rat striatum about the effects of morphine on uptake and release of C-14-dopamine.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R52, 1977.

Studies in vitro of the effects of morphine and various other drugs on the uptake and release of radiolabeled dopamine (DA) in rat striatum synaptosomes are reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft held in Mainz, Germany, in March 1977. The uptake of DA was significantly inhibited by 2,4-dinitrophenol and low temperature and reduced by imipramine, dextroamphetamine, and chlorpromazine. Neither ethanol nor morphine affected DA uptake; however, morphine significantly inhibited the potassium induced release of radioactivity. 1 references. (Author abstract modified)

003105 Brookman, Sheldon; Kourounakis, Panos. Institut de medecine et de chirurgie experimentales, Universite de Montreal, Montreal, Quebec H3C 3J7, Canada **Influence of imipramine and various steroids on hepatic in vitro N-demethylation of tricyclic antidepressants.** Research Communications in Chemical Pathology and Pharmacology. 16(4):757-760, 1977.

The effects of equimolar doses of imipramine (IP) and three catatoxic steroids, pregnenolone-16alpha-carbonitrile, spironolactone, and dexamethasone on hepatic mixed function oxidases were investigated in female rats. Liver weight and N-demethylation of IP and amitriptyline were significantly increased by 3 days of catatoxic steroid pretreatment. Repeated prior administration of IP enhanced N-demethylase activity and 9000g supernate protein, but diminished hepatic weight. All the compounds tested are potent drug metabolizing enzyme inducers, the most active being dexamethasone. 14 references. (Author abstract modified)

003106 Brooks, D. C.; Gershon, M. D. Dept. of Anatomy, Cornell University Medical College, 1300 York Ave., New York, NY 10021 **Amine repletion in the reserpinized cat: effect**

upon PGO waves and REM sleep. Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(1):35-47, 1977.

Selective repletion of 5-HT and catecholamines in the reserpinized cat was used to study the role of these biogenic amines in the regulation of ponto-geniculo-occipital (PGO) wave activity and sleep. Results suggested that 2 neuronal systems, one employing 5-HT and the other catecholamines, play a part in the regulation of PGO lateral geniculate waves and, presumably, PGO -- rapid eye movement sleep. The 5-HT system may be primarily responsible for suppressing PGO/REM during slow wave sleep, with the catecholamine system playing a comparable part during wakefulness. Earlier reports that L-Dopa induces REM sleep in the reserpinized animal were not confirmed, indicating that the postulated role of catecholamines in the induction of this state should be reevaluated. 34 references. (Author abstract modified)

003107 Burns, David; London, Jack W.; Brunswick, David J.; Pring, Martin; Mendels, Joe; Garfinkel, David; Rabinowitz, Joseph L. Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104 **A study of the relationship between brain serotonin metabolism and lumbar fluid 5-hydroxyindoleacetic acid.** In: Brady, J., Psychiatry: areas of promise and advancement. New York, Spectrum, 1977. 253 p. (p. 53-64).

To elucidate the relationships between brain serotonin metabolism and 5-hydroxyindoleacetic acid (5HIAA) in various regions of the cerebrospinal fluid (CSF) of the rat, kinetic analysis of 5HIAA from brain tissue and CSF of the rat after its injection into the lateral ventricle was undertaken and the data then analyzed with a computer aided mathematical modeling system. Based on transport constants and volume and flow parameters a steady state exchange model was developed which indicated that 5HIAA in brain and ventricles were in rapid equilibrium and that the net rate of 5HIAA trasnport from brain to ventricles equals the rate of serotonin turnover by the brain. The 5HIAA was excreted from the CSF into blood: 40% via the active transport system of the ventricles; 60% from the extraventricular subarachnoid spaces by bulk flow and active transport. Results suggest that there is no direct brain to blood 5HIAA transport in the rat. Simulation of a probenecid test suggested that the increase in brain 5HIAA concentration following probenecid is a consequence of the rapid equilibrium between brain tissue and ventricular fluid. Implications of findings for clinical research in depression and neurochemistry are discussed. 27 references.

003108 Carr, Rosemary H.; Ipaktchi, Mehdi; Thenen, Shirley W. Department of Nutrition, Harvard School of Public Health, Boston, MA 02115 **Effects of prolonged fenfluramine administration in obese and nonobese mice.** Proceedings of the Society for Experimental Biology and Medicine. 154(1):116-120, 1977.

The effects of prolonged oral administration of fenfluramine (FEN) were studied in genetically obese (ob/ob) mice, mice made hyperphagic and obese by gold thioglucose injections (GTG), and in nonobese mice. Administration of FEN for 8 weeks reduced food intake and body weight in all 3 groups. FEN reduced plasma glucose in the ob/ob mice at both the 6th and 8th weeks of treatment under fed and fasted conditions, respectively. FEN significantly reduced plasma glucose in fed, but not in fasted, GTG mice, and not in nonobese mice. FEN significantly reduced plasma insulin in the normally hyperinsulinic ob/ob mice only during the last weeks when body weight was also reduced and plasma insulin was not significantly affected in GTG and nonobese mice. FEN lowered plasma triglyceride in all animals, but only significantly in GTG mice. FEN did not affect liver glycogen or reduce the percentage of body fat in any group. The results indicate the direct hypoglycemic action of FEN and suggest that FEN does not enhance weight loss by enhancing lipolysis in adipose tissue. 19 references.

003109 Carruba, Michele O.; Picotti, Giovanni B.; Zambotti, Fernanda; Mantegazza, Paolo. Dept. of Pharmacology, School of Medicine, Univ. of Milan, Via Vanitelli 32, I-20129, Milan, Italy **Blockade by mazindol of brain 5-HT depletion induced by p-chloromethamphetamine.** Journal of Pharmacy and Pharmacology (London). 29(4):242-243, 1977.

The possible inhibition of brain 5-hydroxytryptamine (5-HT) depletion caused by p-chloromethamphetamine (pCMA) by mazindol or chlorimipramine was studied in rats. It was found that mazindol and chlorimipramine were both equally potent in antagonizing brain 5-HT depletion, but unlike chlorimipramine, mazindol was not found to reduce brain 5-hydroxyindoleacetic acid concentrations. 17 references.

003110 Carson, S.; Godwin, S.; Massoulie, J.; Kato, G. Laboratoire de Neurobiologie, Ecole Normale Superieure, F-75005 Paris, France **Solubilisation of atropine-binding material from brain.** Nature (London). No. 5598:176-178, 1977.

The solubilization with 2M sodium chloride of an atropine binding material from the ox cerebral cortex, which has properties similar to those found for the muscarinic receptor in subcellular preparations, is reported. The high affinity binding of labelled atropine to a crude synaptosomal preparation isolated from the cerebral cortex could be displaced by unlabelled atropine, scopolamine, lachesine and quinuclidinylbenzilate (QNB). Estimates of inhibition binding constants of these antagonists together with those of agonists determined in the study agreed closely with those reported by others except that QNB showed two distinct affinities. Acetylcholine, acetyl-beta-methylcholine, oxotremorine and carbamylcholine gave biphasic curves for inhibition of atropine binding. A single binding constant was found for pilocarpine and arecoline; choline was ineffective up to millimolar concentrations. The inhibition constant values for both agonists and antagonists agreed well with those reported for subcellular brain preparations and with the agonist binding associated with smooth muscle contraction. After treatment of a crude synaptosomal preparation with 2M sodium chloride and separation of the solubilized material by centrifugation, binding of 3H-atropine could be detected in the solubilized fraction by a filtration assay. The solubilized material contained a single, high affinity binding site for agonists. Antagonists bound to the soluble fraction with QNB being the most active followed by scopolamine, atropine and lachesine but in a sigmoidal fashion and with lower affinities than to the membrane preparations. The results suggest that the solubulized material which shows specific atropine binding was derived from the high affinity component of the membrane preparation which is most likely to be the muscarinic receptor site. 15 references.

003111 Catravas, George N.; Takenaga, June; McHale, Carolyn G. Armed Forces Radiobiology Research Institute, Bethesda, MD 20014 **Effect of chronic administration of morphine on monoamine oxidase activity in discrete regions of the brain of rats.** Biochemical Pharmacology (Oxford). 26(3):211-214, 1977.

The effects of chronic administration of morphine on the activity of monoamine oxidase (MAO) in the thalamus, hypothalamus, hippocampus, cerebellum and cerebral cortex of the rat brain was investigated. Shortly after the last ad-

ministration of morphine, brain MAO (EC 1.4.3.4) was drastically reduced in all areas studied of the brains of rats in which chronic morphine administration induced a hyperactivity syndrome manifested by compulsive gnawing and spasmodic jumping. The lowest values were seen at approximately 30 min and they returned to nearly normal levels by 6 h after the last injection. In contrast, no significant changes were observed in the activity of the enzyme in animals that did not exhibit this syndrome after morphine administration. 29 references. (Author abstract modified)

003112 Cherkin, Arthur; Eckardt, Michael J. Psychobiology Research Laboratory, Veterans Administration Hospital, Sepulveda, CA 91343 **Effects of dimethylaminoethanol upon life-span and behavior of aged Japanese quail.** Journal of Gerontology. 32(1):38-45, 1977.

The effects of dimethylaminoethanol upon the lifespan and behavior of aged Japanese quail were investigated, based on the lysosome hypothesis of aging which predicts that membrane stabilizers will extend lifespan. Stabilizers containing the dimethylaminoethanol moiety (DMAE) have been reported to extend the lifespan of drosophila and mice. Japanese quail were administered DMAE bitartrate in the drinking water for 69 weeks, starting at 195 weeks of age. A matched control group (N=14) received tartaric acid in the water. Contrary to the prediction, the DMAE treated group had a shorter lifespan after start of treatment (49 weeks) than the controls (69 weeks). No significant differences between the groups were observed in bodyweight or daily fluid intake. Three behavioral studies were carried out on survivors at 243 to 249 weeks of age, namely; activity response to light flash; sexual mounting reponse to a female quail; and classical conditioning of the heartrate. Aged quail differed from young adults in changes in motor activity in response to light flashes. Aged quail appeared less responsive initially to reinforced conditioning trials and demonstrated extinction when light flash was not followed by electric shock. There were no detectable differences in latency to mount or in basal heartrate, either as a function of age or as a function of DMAE treatment. 29 references. (Author abstract)

003113 Chou, Dorothy T.; Wang, S. C. Department of Pharmacology, Nutrition and Health Science, General Foods Corporation Technical Center, Tarrytown, NY **Unit activity of amygdala and hippocampal neurons: effects of morphine and benzodiazepines.** Brain Research (Amsterdam). 126(3):427-440, 1977.

The effects of morphine sulfate and two benzodiazepine derivatives, chlordiazepoxide HCl and diazepam, were evaluated on single unit activity of the amygdaloid nuclear complex and hippocampal formation in immobilized cats. Chlordiazepoxide HCl or diazepam suppressed spontaneous firing rates of the amygdala and the hippocampal neurons. In contrast, the spontaneous firing rates of neurons in these limbic structures were augmented by morphine sulfate. The morphine induced augmentation of hippocampal neuronal activity was effectively antagonized by naloxone but naloxone only partially suppressed the morphine induced augmentation of amygdala neuronal activity. In a dose dependent fashion, chlordiazepoxide and diazepam administration prevented or antagonized morphine induced augmentation of amygdala and hippocampal neuronal activity. Results suggest that, in the cat, the amygdala and hippocampus may play an important role for morphine induced behavioral responses. Moreover, the data imply that these two limbic structures may be the sites of tranquillizing actions of diazepam and chlordiazepoxide. 31 references. (Author abstract)

003114 Christensen, Sten; Geisler, Arne; Badawi, Ibrahim; Madsen, Stig Nistrup. Department of Pharmacology, University of Copenhagen, 20 Juliane Mariesvej, DK-2100 Copenhagen, Denmark **Plasma and urinary cyclic AMP levels in normal and lithium-treated rats.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(3):455-459, 1977.

In a letter to the editor, plasma and urinary adenosine 3',5'-monophosphate (cAMP) levels were reported for normal and lithium (Li) treated rats. Li was given in the diet for 60 to 90 days; all Li treated animals developed polyuria as noted from their increased water consumption. Li treatment caused a small but significant increase in plasma cAMP levels, but did not significantly change 24 hr cAMP excretion. The urinary cAMP to creatinine ratio was decreased by Li, but this was partly due to a higher rate of creatinine excretion in Li treated rats. The Li treated rats also consumed more food, and their urine flow was 8 time higher than that of controls. The results indicate that the increase in plasma cAMP induced by Li was a consequence of a lowering of the renal clearance, and do not support the theory that Li ions at therapeutic levels inhibit cAMP formation by tissues in general. 20 references.

003115 Chu, C. K.; Stella, V. J.; Bruckner, J. V.; Jiang, W. D. School of Pharmacy, University of Kansas, Lawrence, KS 66045 **Effects of long-term exposure to environmental levels of polychlorinated biphenyls on pharmacokinetics of pentobarbital in rats.** Journal of Pharmaceutical Sciences. 66(2):238-241, 1977.

The effects of environmental levels of a contaminant and enzyme inducer, a polychlorinated biphenyl, on the pharmacokinetics of pentobarbital, a drug whose primary elimination route is liver metabolism, was investigated in rats. After 35 days of pretreatment with 25 ppm of the contaminant in food, a significant acceleration of pentobarbital elimination was observed. After 70 days and 140 days of pretreatment, animals receiving either 5ppm or 25ppm of the contaminant in food showed significant acceleration of pentobarbital elimination. Calculation of total body clearance suggested that pentobarbital elimination in the rats had approached portal blood flow rate limited metabolism. 29 references. (Author abstract modified)

003116 Cicero, Theodore J.; Bell, Roy D.; Meyer, Edward R.; Schweitzer, John. Department of Psychiatry, Washington University School of Medicine, 4940 Audubon Avenue, St. Louis, MO 63110 **Narcotics and the hypothalamic-pituitary-gonadal axis: acute effects on luteinizing hormone, testosterone and androgen-dependent systems.** Journal of Pharmacology and Experimental Therapeutics. 201(1):76-83, 1977.

The effects of narcotics were examined in the male rat to clarify whether their effects on testosterone levels represent direct actions on the testes or whether they are secondary to a primary effect on the hypothalamic/pituitary axis. The results indicate that a large number of narcotics acutely depress serum luteinizing hormone levels and that these reduced gonadotropin levels lead to a subsequent fall (1 or 2 hours later) in serum testosterone levels. The luteinizing hormone depleting effect of the narcotics appeared to represent a specific narcotic action since the (-)-isomers of the narcotics were much more effective than the (+)-isomers, naloxone antagonized their effects and tolerance rapidly developed. It is suggested that the impairment of the functional and structural integrity of the secondary sex organs produced by chronic narcotic administration is not due to a direct effect of these drugs since they have no effect on the uptake of subcellular distribution of testosterone in the secondary sex organs or on the an-

drogen dependent accumulation of myoinositol. It is also suggested that the testosterone depletion produced by the narcotics is solely responsible for their adverse effect on the secondary sex organs. It is posited that the effects of the narcotics on the hypothalamic/pituitary gonadal axis are confined to either the hypothalamus or the pituitary gland. 37 references. (Journal abstract modified)

003117 Cott, Jerry; Engel, Jorgen. Department of Pharmacology, University of Goteborg, S-40033 Goteborg, Sweden **Antagonism of the analeptic activity of thyrotropin-releasing hormone (TRH) by agents which enhance GABA transmission.** Psychopharmacology (Berlin). 52(2):145-149, 1977.

To examine the role of gamma-aminobutyric acid (GABA) containing pathways in mediating the analeptic effects of thyrotropin releasing hormone (TRH), aminooxyacetic acid (AOAA), gamma-hydroxybutyric acid (GHBA), and baclophen agents which enhance GABA transmission were administered to mice. Administration of TRH to mice reduced the sleep and hypothermia induced by ethanol. However, TRH did not reduce the sleep of mice that were given GHBA, baclophen, or AOAA in combination with ethanol. TRH also failed to reverse the hypothermia induced by the combination of ethanol and baclophen or GHBA, and the characteristic neurological effects of TRH (e.g. tremor, increased muscle tone, and increased respiratory rate) were reduced. TRH induced locomotor stimulation was prevented by pretreatment with small doses of AOAA, GHBA, and baclophen. While TRH reduced the hypothermia produced by large doses of the three drugs, it did not antagonize the locomotor retardation produced by baclophen or GHBA. A hypothesis that the analeptic effects of TRH may be mediated via an inhibition of GABA systems is discussed. 36 references. (Author abstract modified)

003118 Cotzias, George C.; Miller, Samuel T.; Tang, Lily C.; Papavasiliou, Paul S. Memorial Sloan-Kettering Cancer Center, New York, NY **Levodopa, fertility, and longevity.** Science. 196(4289):549-551, 1977.

High concentration of the dopaminergic drug levodopa (L-dopa,L-3,4-dihydroxyphenylalanine) were administered to mice in their diet in order to study the effect of the drug on longevity and the aging process. Fertility was affected to a moderate degree, and the mean life span was prolonged by a maximum of 50%. The results are compatible with those of earlier research concerning humans who received the drug as a treatment for Parkinson's disease. 15 references. (Author abstract modified)

003119 Dadkar, N. K.; Dohadwalla, A. N.; Bhattacharya, B. K. Department of Pharmacology, Research Centre, Hoechst Pharmaceuticals Ltd., Mulund, Bombay 400 080, India **Possible role of dopamine in central effects of cocaine as measured by apomorphine gnawing test in mice.** Psychopharmacology (Berlin). 52(2):115-117, 1977.

The role of dopaminergic and noradrenergic systems in apomorphine induced gnawing by cocaine was studied in mice by using various pharmacological agents known to modify synthesis and storage of dopamine and noradrenaline. Apomorphine did not induce a compulsion to gnaw, but pretreatment with cocaine caused gnawing activity. The effect of cocaine was inhibited by pretreatment with alpha-methyl-para-tyrosine, haloperidol, and physostigmine, but not with bis(4-methyl-l-homopiperazinylthiocarbonyl) disulfide (FLA-63), phenoxybenzamine or tetrabenazine. The findings suggest that a dopaminergic mechanism plays a significant role in the potentiation of apomorphine gnawing activity by cocaine and also support the view that inhibition of dopamine uptake is responsible for the stimulatory action of cocaine. 15 references. (Author abstract modified)

003120 Daniel, P. M.; Pratt, O. E.; Wilson, Penelope A. Dept. of Applied Physiology and Surgical Science, Royal College of Surgeons, Lincoln Inn Fields, London WC2A 3PN, England **The exclusion of L-isoleucine or of L-leucine from the brain of the rat, caused by raised levels of L-valine in the circulation, and the manner in which this exclusion can be partially overcome.** Journal of the Neurological Sciences (Amsterdam). 31(3):421-431, 1977.

The way in which a raised level of L-valine (Val) in the circulation partially excludes L-isoleucine (Iso) and L-leucine (Leu) from entering the rat brain, and how this exclusion can be partially overcome was investigated. High concentrations of Val in the plasma reduced the influx both of Iso and Leu into the brain to 10 to 15% of the normal, suggesting that the three amino acids compete for a shared transport carrier for entry into the brain. The exclusion of Iso and Leu was partially overcome by simultaneously raising the concentration of Iso or of Leu in the circulation. The results indicate the important role played by a saturable shared carrier mediated transport system in ensuring that an adequate supply of these amino acids reaches the brain from the circulation during life. It was suggested that Iso might be given, with advantage, in the diets of some patients suffering from maple syrup urine disease or hypervalinaemia. 22 references.

003121 Darwish, Susan A. E.; Furman, Brian L. Department of Physiology and Pharmacology, University of Strathclyde, George Street, Glasgow, GI IXW, Scotland **Effects of levodopa and dopamine on plasma glucose concentration in mice.** European Journal of Pharmacology (Amsterdam). 41(4):351-360, 1977.

The effects of levodopa and dopamine (DA) on plasma glucose concentration, insulin secretion, and plasma free fatty acid (FFA) concentration were examined in mice. Levodopa produced a dose dependent hypoglycemic response in nialamide treated, fasted mice and in pargyline treated mice, but not in mice which were not treated with a monoamine oxidase inhibitor. DA did not affect plasma glucose under these conditions. Levodopa and DA produced hypoglycemia when injected intracerebroventricularly. The DA antagonists haloperidol and pimozide as well as cyproheptadine and methysergide blocked the hypoglycemic response to levodopa. Hypoglycemia was also produced by 5-hydroxytrytophan (5-HTP) and by icv 5-hydroxytryptamine (5-HT). p-Chlorophenylalanine reduced the response to levodopa as well as to 5-HTP and 5-HT. Levodopa induced hypoglycemia does not appear to involve stimulation of insulin secretion since plasma immunoreactive insulin levels were not increased, plasma FFA was elevated, and liver glycogen content was not significantly altered by levodopa. It is suggested that the hypoglycemic response to levodopa is mediated through DA in the brain, although the involvement of 5-HT in the response and the mechanisms involved remain to be determined. 26 references. (Author abstract modified)

003122 David, Joy; Kaul, C. L.; Grewal, R. S. CIBA-GEIGY Research Centre, Bombay 400063, India **Effect of intracaudate drug injections on the striatal syndrome in reserpinized cats.** Neuropharmacology (Oxford). 16(3):1679-1689, 1977.

The ability of a variety of drugs to antagonize various aspects of the reserpine induced striatal syndrome in cats, consisting of progressively increasing motor signs of hypokine-

sia, rigidity, catatonia and tremor, was studied. After injection into the caudate nucleus, apomorphine completely reversed reserpine induced motor signs, while dopamine (DA), L-DOPA, dextroamphetamine, atropine and amantadine significantly reduced various aspects of the extrapyramidal symptoms. L-DOPA produced almost complete reversal of extrapyramidal symptoms when given systemically rather than after intracaudate injection. Equiactive doses of clonidine antagonized only reserpine induced eye changes without significantly influencing extrapyramidal symptoms, while 5-hydroxytryptamine, pyribenzamine, physostigmine and tremorine were ineffective. Electromyelogram assessment of rigidity and polygraphic recording of EEG and tremor together with neurochemical analysis of caudate nucleus DA levels, following apomorphine and DA in reserpinized cats, provides supporting evidence for apomorphine's activating role on DA receptors in the striatum. 30 references. (Author abstract modified)

003123 de Boer, Thijs; Metselaar, Herold J.; Bruinvels, Jacques. Department of Pharmacology, Erasmus University Rotterdam, P.O. Box 1738, Rotterdam, The Netherlands **Suppression of GABA-induced abstinence behaviour in naive rats by morphine and bicuculline.** Life Sciences. 20(6):933-942, 1977.

The suppression of gamma-aminobutyric acid (GABA) induced abstinence behavior in naive rats by morphine and bicuculline was studied. Injection of n-dipropylacetate (DPA) in naive rats produced abstinence behavior including shaking, digging, hunchback posture, piloerection and ptosis during 15 min and increased motor activity considerably. A subconvulsive dose of the GABA antagonist bicuculline suppressed the DPA induced abstinence behavior, indicating that GABA was increased at receptor sites. Morphine in a low dose suppressed the abstinence behavior, and naloxone administered after morphine released the abstinence behavior. Simultaneous treatment with morphine and naloxone or naloxone alone had no effect. Administration of higher doses of morphine to DPA treated rats resulted in a severe depression of motor activity. It was concluded that an increased availability of GABA at its receptor sites played an important role in the behavior observed after DPA administration. The morphine and naloxone experiments suggest that morphine receptors are involved in DPA induced abstinence behavior. 22 references. (Author abstract modified)

003124 Deckard, Betty. Psychogenetics Unit, Brentwood, CA 94513 **Genetic, biochemical, and pharmacological correlates of responses to priming in mice.** Behavior Genetics. 7(1):52-53, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, genetic, biochemical, and pharmacological correlates of responses to priming in mice were studied with respect to audiogenic seizures not specific to interval. Animals selected for susceptibility to priming induced seizures were not susceptible to spontaneous audiogenic seizures, suggesting independent genetic mechanisms in the mediation of phenotypes. Acoustic priming did not significantly affect subsequent tests of electroconvulsive seizure susceptibility in selectively bred mice, but there were significant differences in electroconvulsive seizures between animals of the priming induced seizure prone, the priming induced seizure resistant, and unselected lines. It was also found that alpha-methyltyrosine, reserpine, and tetrabenazene did not enhance priming induced audiogenic seizures in the priming induced seizure resistant line; however chlorpromazine, iproniazid, 5-hydroxytryptophan, amphetamine, and aminooxyacetic acid protected both priming induced seizure prone and unselected animals from priming induced seizures; and aminooxyacetic acid did not prevent priming but puromycin did. (Author abstract modified)

003125 Denizeau, Francine; Sourkes, T. L. Department of Psychiatry and Biochemistry, McGill University, Montreal, Quebec, Canada **Regional transport of tryptophan in rat brain.** Journal of Neurochemistry (Oxford). 28(5):951-959, 1977.

Tryptophan uptake was studied in brain slices and synaptosomes prepared from regions known to vary in the numbers of serotonergic cell bodies and nerve endings that they contain. The rate of tryptophan uptake was highest in hypothalamus for both types of preparation. Differences among the regions were much more pronounced in isolated nerve endings (synaptosomes). Loading with tryptophan did not affect the uptake into tissue slices. Tryptophan accumulation in hypothalamus synaptosomes was reduced after intraventricular injection of 5,7-dihydroxytryptamine whereas no change was observed in synaptosomes prepared from cerebellum under the same conditions; accumulation by synaptosomes prepared from the hypothalamic and hippocampal regions was reduced after raphe lesions. 26 references. (Author abstract)

003126 Desaiah, Durisala; Ho, Ing K. Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS 39216 **Effect of morphine on mouse brain ATPase activities.** Biochemical Pharmacology (Oxford). 26(1):89-92, 1977.

The effects of morphine on adenosine triphosphatase (ATPase) activity was investigated in mouse brain after acute and chronic morphine administration and after naloxone induced withdrawal. Acute administration was s.c. and chronic administration was via pellet implantation. Mouse brain tissue was homogenized and fractionated for analysis. Naloxone was administered, where applicable, prior to sacrifice. Results indicate that dopamine and norepinephrine enhanced the sodium and potassium ion ATPase activity in naive but not in morphine tolerant dependent mouse brain. The dopamine stimulatory effect was not observed in chronic morphine treated mice. 13 references.

003127 Dismukes, Key; Mulder, Arie H. Department of Pharmacology, Free University, Medical Faculty, v.d. Boechorststraat 7, Amsterdam-1011, The Netherlands **Effects of neuroleptics on release of 3H-dopamine from slices of rat corpus striatum.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(1):23-29, 1977.

The effects of neuroleptics on the release of 3H-dopamine (DA) from slices of rat corpus striatum were studied. The butyrophenones, haloperidol and spiroperidol, increased basal tritium efflux in a dose dependent manner. The phenothiazines, chlorpromazine and fluphenazine, were much less effective. The butyrophenones strongly inhibited the electrically stimulated overflow of both DA and 14-C-gamma-aminobutyric acid, while the phenothiazines had little effect. The action of haloperidol on DA release could be blocked by cocaine, but not by apomorphine. Apomorphine itself had no significant effect on DA release. It is suggested that different mechanisms may be involved in the local presynaptic receptor mediated feedback regulation of transmitter release in noradrenergic and dopaminergic systems in the central nervous system. 18 references. (Author abstract modified)

003128 Doggrell, S. A.; Woodruff, G. N. Dept. of Physiology and Biochemistry, University of Southampton, Bassett Crescent East, Southampton S09 3TU, England **Effects of an-**

tidepressant drugs on noradrenaline accumulation and contractile responses in the rat anococcygeus muscle. British Journal of Pharmacology (London). 59(3):403-409, 1977.

The effect of a series of antidepressant drugs on noradrenaline accumulation was studied in the isolated anococcygeus muscle of the rat. The most potent inhibitors of noradrenaline accumulation were nortriptyline, desipramine and protriptyline, desipramine and protriptyline. Other uptake inhibitors were less active in potentiating the noradrenaline response. Nortriptyline, in concentrations that potentiated the action of noradrenaline, reduced or abolished the response to tyramine. (Author abstract)

003129 Duggan, A. W.; Hall, J. G. Dept. of Pharmacology, Australian National University, Canberra, Australia **Morphine, naloxone and the responses of medial thalamic neurones of the cat.** Brain Research (Amsterdam). 122(1):49-57, 1977.

Morphine and naloxone were administered both electrophoretically and intravenously, and spontaneous and evoked firing, the chemical sensitivity of neurons of the nucleus lateralis posterior, and center median parafascicularis complex were studied to examine the different responses of medial thalamic neurons of the cat to morphine and naloxone. Administered electrophoretically, morphine depressed the firing of medial thalamic neurons. This effect was not antagonized by naloxone which itself was a depressant. A long-lasting increase in sensitivity to L-glutamate followed ejection of both morphine and naloxone. Intravenous morphine had inconstant effects on spontaneous firing and that evoked by electrical stimulation of the forepaws, but in 7 of 10 experiments reduced the sensitivity of neurons to L-glutamate. This effect was reversed in all cases by intravenous naloxone. 22 references. (Author abstract modified)

003130 Duhault, Jacques; Boulanger, Michele. Department of Biochemical Pharmacology, Institut de Recherches Servier, 14 Rue du Val d'Or, F-92150, Suresnes, France **Fenfluramine long-term administration and brain serotonin.** European Journal of Pharmacology (Amsterdam). 43(2)203-205, 1977.

The effects of long-term administration of fenfluramine on the brain serotonergic system of rats was studied. Fenfluramine induced a decrease of brain 5-HTP to the same extent as did an acute dose of the drug. The brain serotonin level returned to the control value 48 n after drug withdrawal. The rapidly reversible decrease of brain 5-HT in long-term treated rats shows that fenfluramine does not induce degenerative lesions of 5-HT neurones as does parachloroamphetamine, a compound which has been shown to remain tightly bound to brain synaptosomes for a long time with a subsequent sustained 5-HT lowering effect. 13 references. (Author abstract)

003131 Ebersole, John S. no address **Initial alterations of neuronal responses during strychnine epileptogenesis in visual cortex.** Neurology. 27(4):338, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, initial alterations of neuronal responses during strychnine (ST) epileptogenesis in the visual cortex of cats were studied. Recurrent on/off stimulation with projected images of optimal configuration was presented during the iontophoresis of ST around cortical area 17 neurons. ST moderately enhanced the number and frequency of spikes in a neuron's extracellular response. Higher rates of ST application often reduced spike number and amplitude. Termination of ST usually was followed by a short lived response increase that could be more prominent than that during iontophoresis. Groups of spikes in a response with latencies longer than primary afferents were preferentially enhanced. Phasic neuronal responses developed, most notably additional later latency spike bursts soon after or simultaneously with an increase in the primary response. These were often multiple and rhythmic. The ST response alterations were precursors of fully developed paroxysmal depolarization shifts, but they differed significantly from those associated with epileptogenesis from penicillin iontophoresis. The results support the hypothesis that suppression of postsynaptic, possibly recurrent, inhibition is one of ST's epileptogenic actions in cortex.

003132 Edelfors, Sven. Department of Pharmacology, University of Copenhagen, 20 Juliane Mariesvej, DK-2100 Copenhagen, Denmark **The influence of lithium on water binding ability, consistency and macromolecules in the rat brain.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(1):126-133, 1977.

The influence of lithium on water binding ability, consistency and macromolecules in the rat brain was investigated in animals fed lithium in the diet for 50 days, 80 days, or 120 days. The treatment caused a significantly more rigid consistency of the brain tissue. The water content and water binding ability in various parts of the brain was unchanged. The content of hexosamine and protein in total brain was significantly decreased after lithium. The content of chondroitin sulfate in various parts of the brain was unchanged, but the content of hyaluronic acid was significantly increased in the cerebellum and in the thalamic area. It is suggested that lithium influences the macromolecules from the extracellular space, causing an alteration of the neuronal function. 15 references. (Author abstract modified)

003133 Enjalbert, A.; Priam, M.; Kordon, C. Unite 159 de Neuroendocrinologie, Centre Paul Broca de l'INSERM, 2ter rue d'Alesia, F-75014 Paris, France **Evidence in favour of the existence of a dopamine-free prolactin-inhibiting factor (PIF) in rat hypothalamic extracts.** European Journal of Pharmacology (Amsterdam). 41(2):243-244, 1977.

An attempt was made to confirm the existence of a prolactin inhibiting factor (PIF) separate from dopamine by assaying in vitro the prolactin inhibiting activity of hypothalamic extracts from which catecholamines were eliminated by absorption on alumina (A1203), and by testing the prolactin inhibiting activity of such A1203 treated or untreated extracts and of dopamine (DA) in the presence of a DA receptor inhibitor. It was found that the addition of 3 mediobasal hypothalamic fragments (MBH) equivalents to pituitary incubates significantly inhibited the in vitro release of prolactin. A comparable inhibition resulted from incubation with DA or with subcellular fractions derived from the MBH. When the DA receptor inhibitor, haloperidol, was added to the incubation medium at a concentration which would not significantly affect prolactin release in control incubates, the prolactin inhibiting effect of DA was almost completely eliminated; in contrast, the prolactin inhibiting activity of the homogenate was only weakly antagonized by the haloperidol. The maintainance of prolactin inhibiting activity in the MBH subcellular fractions after absorption of catecholamines, as well as the failure of haloperidol to significantly antagonize the effects of PIF in these fractions, strongly support the hypothesis that another hypothalamic factor besides DA can inhibit the release of prolactin from the pituitary. 5 references.

003134 Enna, S. J.; Collins, James F.; Snyder, Solomon H. Dept. of Neurobiology and Anatomy, University of Texas Medical School at Houston, PO Box 20708, Houston, TX 77025 **Stereospecificity and structure-activity requirements of GABA receptor binding in rat brain.** Brain Research (Amsterdam). 124(1):185-190, 1977.

The influence of bicuculline methochloride isomers, other potential GABA antagonists, and muscimol were examined on synaptic receptor binding for GABA in rat brain preparations to investigate structure/activity requirements. The alkaloid muscimol was quite potent in displacing specifically bound tritiated GABA. The dextrorotatory isomer of bicuculline methochloride, which is 400 times more potent a convulsant than the levorotatory isomer, was also much more potent in reducing GABA receptor binding. In contrast to the stereospecificity of the isomers on sodium independent GABA receptor binding, there was no difference between the bicuculline isomers in their ability to inhibit sodium dependent tritiated GABA binding, tritiated haloperidol binding to the dopamine receptor, and tritiated quinuclidinyl benzilate binding to the cholinergic muscarinic receptor. Picrotoxinin and picrotoxin failed to inhibit GABA receptor binding. It is suggested that the selective stereospecificity of bicuculline influences on GABA receptor binding further supports the idea that the sodium independent binding of tritiated GABA to membrane fractions of mammalian brain involves the physiological synaptic receptor for GABA. 17 references.

003135 Erdosova, R.; Kraus, M.; Rehulka, J. Institute of Physiology, Czechoslovak Academy of Sciences, 142 20 Prague 4, Czechoslovakia **Influence of stress and phenobarbital on corticosterone metabolism during early postnatal life of rat.** Life Sciences (Oxford). 20(3):459-466, 1977.

Male rats were preexposed to stress or phenobarbital to determine the influence on corticosterone metabolism during early postnatal life. Rats were pretreated twice daily for 3 days by physiological saline i.p. (stress) or by phenobarbital (20mg/kg). Perinatally, both stress and phenobarbital decrease corticosterone side chain metabolism while no change was observed in A ring reduction rate. In older animals no effect of the stress on corticosterone metabolism was observed. The inhibitory influence of phenobarbital on the side chain metabolism was still apparent at age of 14 days, but not in adult animals. The A ring reduction rate was increased by phenobarbital at age of 14 days and in adult animals. Measurements of serum corticosterone and corticosterone production by adrenal glands in vitro confirmed earlier reports showing that during perinatal period increased level of circulating corticosterone can be associated with minor or transient changes in adrenal cortex activity. It is concluded that changes in liver corticosterone metabolism are likely to play an important role in regulation of glucocorticoid activity perinatally when the responsiveness of pituitary adrenal system to environmental stimuli is decreased. 38 references. (Author abstract modified)

003136 Escueta, A. V.; Victor, S.; Davidson, D.; Tainer, B. no address **The effects of electroshock convulsions on 45Ca++ uptake and release in synaptic terminals.** Neurology. 27(4):337, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the effects of electroshock convulsions on 45-calcium (Ca) uptake and release were studied in synaptic terminals from cerebral cortices of rats. After 4 and 6 days of electroshock convulsions, Ca content of synaptosomes rose 20 and 37 percent, respectively. After 6 days of electroshock convulsions, Ca uptake from shocked and control rats was time dependent, maximal at 3mM adenosine triphosphate (ATP), inhibited by sodium, dinitrophenol, potassium cyanide, and N-ethylmaleimide, and markedly enhanced by glutamate. Glutamate and electroshock seizures did not affect the distribution of 45-Ca; 65 percent resided in synaptic plasma membranes after osmotic lysis. Six mM ATP reduced Ca outflux 35 percent more in electroshocked rats than in controls. Sodium enhanced Ca outflux 4 to 8 times in controls and shocked rats. The results show that repeated depolarizations increase Ca content within synapses by decreasing the Ca outflux process.

003137 Fairman, K.; Chiappinelli, V.; Giacobini, E.; Yurkewicz, L. Laboratory of Neuropsychopharmacology, Dept. of Biobehavioral Sciences, University of Connecticut, Storrs, CT 06268 **The effect of a single dose of reserpine administered prior to incubation on the development of tyrosine hydroxylase activity in chick sympathetic ganglia.** Brain Research (Amsterdam). 122(3):503-512, 1977.

The effects of preincubation injections of reserpine into the yolk sac of chicken eggs on the development of enzyme activities related to neurotransmitter biosynthesis in chick autonomic ganglia were examined. Reserpine produced a significant increase of tyrosine hydroxylase (TH) activity over controls at 21 days of incubation and a second increase between day 14 and 30 after hatching. Cholineacetyltransfease (ChAc) and dopadecarboxylase (DDC) were not modified in the two periods of increased TH activity. Reserpine had no effect on cholinergic parasympathetic synapses and neurons in the ciliary ganglion, as judged by ChAc activity. When reserpine was acutely administered in three different posthatching periods only the injection at the latest period (days 26 and 27) caused a significant increase in TH activity at day 30. Selective blockade of postsynaptic nicotinic receptors by injections of chlorisondamine almost completely abolished the reserpine induced increase of TH activity at day 15 after hatching. The present results support the view that the development of enzyme activities specifically related to neurotransmitter biosynthesis in chick autonomic ganglia is regulated not only by transsynaptic influences but also by regulator inputs originating in the periphery. 38 references. (Author abstract modified)

003138 Faraj, B. A.; Dayton, P. G.; Camp, V. M.; Wilson, J. P.; Malveaux, E. J.; Schlant, R. C. Department of Radiology, Emory University School of Medicine, 467 Woodruff Memorial Bldg., Atlanta, GA 30322 **Studies of the fate of tyramine in dogs: the effect of monoamine oxidase inhibition, portafemoral shunt and coronary artery ligation on the kinetics of tyramine.** Journal of Pharmacology and Experimental Therapeutics. 200(2):384-393, 1977.

The effects of monoamine oxidase inhibition, portafemoral shunt and coronary artery ligation on the kinetics of tyramine (T) in dogs and the plasma levels of T in patients with myocardial infarction were studied. After administration of T.HCl there was a rapid decline in T plasma levels with an average half-life of 4.3min. Pretreatment with a monoamine oxidase inhibitor (pargyline) resulted in a decrease in T metabolism. This was followed by an increase in the endogenous plasma T. Similar results were obtained in dogs with portafemoral shunt. Coronary artery ligation resulted in an increase in the level of T in the infarcted region with no change in plasma levels. No difference in plasma concentration of T was demonstrated in patients with myocardial infarction compared to those of adult volunteers. 50 references. (Author abstract modified)

003139 Fatome, Marc; Gaudefroy, Alain; Laval, Jean-Denis; Andrieu, Louis; Sentenac-Romanou, Henri. Division d'Hygiene Atomique, Centre de Recherches du Service de Sante des Armees, F-92140 Clamari, France **/Diazepam: radioprotective action and effect on toxicity and radioprotective power of cysteamine./** Le Diazepam: action radioprotectrice et influence sur la toxicite et le pouvoir radioprotecteur de la cysteamine. European Journal of Medicinal Chemistry (Paris). 12(1):93-95, 1977.

The radioprotective action of diazepam and its effect on the toxicity and radioprotective action of cysteamine were studied in mice subjected to 55 to 60 R/mn of radiation from a cobalt 60 source. The 30 day survivors decreased from 95% to 40% when the interval between diazepam injection and irradiation was increased from 15 min to 6 hr. The weak radioprotective action of diazepam was explained by its action on the central nervous system, particularly, by its anticonvulsant action. Pretreatment with diazepam reduced cysteamine toxicity and enhanced its radioprotective activity. 11 references.

003140 Fernandes, M.; Kluwe, S.; Coper, H. Institut fur Neuropsychopharmakologie, Freie Universitat Berlin, Ulmenallee 30, D-1000 Berlin 19, Germany **Quantitative assessment of tolerance to and dependence on morphine in mice.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(1):53-60, 1977.

Methods for the quantitative assessment of tolerance to and dependence on morphine were tested in mice. Tolerance to morphine induced analgesia (hot plate and acetic acid writhing test), hypothermia and lethality were quantified by measuring the degree of parallel shifts of semilog, dose response relationships induced by repeated opioid administration. A similar procedure was used for the quantification of nalozone induced withdrawal as an indicator of dependence. The intensity of tolerance development with respect to time of administration and dosage of morphine varied with the test procedure. It was closely parallel, however, in both analgesic tests during acquisition of tolerance. Log/log/linear relationship existed between tolerance in analgesic tests and physical dependence as determined by naloxone induced withdrawal. The minimum tolerance inducing dose of morphine in different tests could not be correlated to the effective dose 50s in the tests. Chronic opiate treatment led to a decrease or an increase in motility response to morphine, depending on the time that had elapsed after the last morphine administration. 23 references. (Author abstract modified)

003141 Flynn, Edward J.; Cerreta, Kenneth V.; Spector, Sydney. Department of Pharmacology, New Jersey Medical School, Nutley, NJ **Pharmacologic response to pentobarbital in actively immunized mice.** European Journal of Pharmacology (Amsterdam). 42(1):21-29, 1977.

The pharmacologic response to pentobarbital (PB) was studied in mice actively immunized by placement on an immunization schedule known to result in the production of antibodies directed against a variety of barbiturates. The response to barbiturate in the immunized mice (IM) and controls was tested using rotarod apparatus for monitoring central nervous system depression. The response to PB in IM was decreased, as reflected by an increase in the time the IM remained on the rotarod and a shift of the dose response curve to the right. There were no large differences between the IM and controls in the liver microsomal activities of NADPH-cytochrome c reductase and aminopyrine N-demethylase or quantities of cytochromes P-450 and b5; although the metharbital N-demethylase activity decreased approximately 30% in IM. The ataxia produced by another depressant agent, ethanol, was not changed in the IM. The results indicate that the decreased pharmacologic response to PB was not the result of changes in levels of the hepatic drug metabolism components, and was selective for barbiturate. 26 references.

003142 Franklin, K. B. J.; Herberg, L. J. Department of Psychology, McGill University, 1205 McGregor Ave., Montreal, Quebec H3A 1B1, Canada **Presynaptic alpha-adrenoceptors: the depression of self-stimulation by clonidine and its restoration by piperoxane but not by phentolamine or phenoxybenzamine.** European Journal of Pharmacology (Amsterdam). 43(1):33-38, 1977.

The suggestion that depression of self-stimulation by clonidine has been ascribed to continuous direct stimulation of alpha-adrenoceptors with consequent disruption of reinforcement signals thought to be conveyed by noradrenergic pathways, was tested by administration of alpha-receptor blocking agents (piperoxane, phentolamine and phenoxybenzamine, PBZ) to rats differing in their affinity for pre and postsynaptic receptor sites. Piperoxane in low doses previously reported to cause specific blockade of presynaptic receptors implicated in negative feedback circuits, caused a significant increase in self-stimulation rate and strongly antagonized the depression of self-stimulation by clonidine. A larger dose or piperoxane and graded doses of phentolamine and PBZ affecting both pre and postsynaptic receptors, depressed self-stimulation, and did not antagonize clonidine induced depression of self-stimulation. It is concluded that depression of self-stimulation by clonidine may depend on clonidine induced inhibition of NA release exerted via presynaptic receptors, and that the effect of clonidine is not necessarily evidence that noncontingent adrenergic stimulation disrupts reinforcement. 16 references. (Author abstract)

003143 Freedman, Robert. Department of Psychiatry, University of Chicago, Chicago, IL **Interactions of antipsychotic drugs with norepinephrine and cerebellar neuronal circuitry: implications for the psychobiology of psychosis.** Biological Psychiatry. 12(2):181-197, 1977.

Using the rat cerebellar Purkinje cell as a model neuronal system, the effects of norepinephrine (NE) and fluphenazine, an antipsychotic drug, are examined. Fluphenazine is shown to be a potent, specific antagonist of the NE mediated inhibition of Purkinje cell discharge. NE, despite its inhibitory action on spontaneous firing of the Purkinje cell, increases its responsiveness to afferent synaptic pathways. These data thus imply that NE may increase the brain's sensitivity to incoming information, and that antipsychotic drugs interfere with this effect. A role for NE, as well as dopamine, in the genesis of psychosis is suggested on the basis of their mutual antagonism by antipsychotic drugs. The facilatory effects of NE on neuronal information processing are used to predict a possible participation of NE in the perceptual difficulties noted in psychosis. 44 references. (Author abstract)

003144 Friedel, Robert O.; Slotnick, Robert N.; Bombardt, Paul A. Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA 98195 **Effects of gamma-aminobutyric acid on 33pi incorporation into rat brain phospholipids in vivo.** Life Sciences (Oxford). 20(2):235-242, 1977.

The effects of gamma-aminobutryic acid (GABA), bicuculline and strychnine on the incorporation in vivo of radiolabeled Pi into phospholipids of rat brain were studied after intracisternal injection of the radionuclide. GABA in-

hibited labeling of phospholipids in the three brain regions was studied. Bicuculline by itself had no significant effect on Pi incorporation, but totally blocked the inhibitory effect of GABA in all three brain regions. Strychnine by itself inhibited phospholipid labeling in the brain stem and forebrain, had no significant effect on GABA inhibition of Pi incorporation in the cerebellum and forebrain, and partially blocked the GABA effect in the brain stem. GABA inhibited Pi incorporation into phosphatidic acid, phosphatidylinositol, phosphatidyl choline and phosphatidyl ethanolamine but had no effect on phosphatidyl serine. It is suggested that the inhibitory effects of GABA on CNS phospholipid labeling are mediated specifically through GABA receptor sites. 19 references. (Author abstract)

003145 Friedhoff, Arnold J.; Miller, Jeannette C. New York University School of Medicine, 550 First Avenue, New York, NY 10016 **In vitro and in vivo studies of extrapineal N-acetyltransferase of rat brain.** Research Communications in Chemical Pathology and Pharmacology. 16(2):225-244, 1977.

A series of experiments was performed in order to: 1) further characterize extrapineal rat brain N-acetyltransferase (NAT); 2) determine the effect of L-isoproterenol, a beta-adrenergic agonist, on the activity of extrapineal NAT; and 3) determine the effect of inhibition of monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) on NAT. It was found that brain NAT has an N-acetylating capacity and a basic pH requirement for optimal activity similar to that of the low activity daytime pineal enzyme. Extrapineal NAT activity was increased by isoproterenol as well as by blockade of MAO and COMT. It is suggested that N-acetylation may be a possible alternative metabolic pathway for biogenic amines and that brain NAT activity may be regulated by a beta-adrenergic mechanism. 30 references.

003146 Friedman, Eitan; Fung, Frederick; Gershon, Samuel. Neuropsychopharmacology Research Unit, New York University School of Medicine, 550 First Ave., New York, NY 10016 **Antidepressant drugs and dopamine uptake in different brain regions.** European Journal of Pharmacology (Amsterdam). 42(1):47-51, 1977.

The effect of tricyclic antidepressants on 3H-dopamine (DP) uptake into synaptosomes of rat striatum and mesolimbic cortical areas were examined. Chlorimipramine (CL) was the most potent uptake inhibitor in both brain regions. Desmethylimipramine, protriptyline (PT) and iprindole (IP) were approximately one half as potent. Benztropine, a known potent inhibitor of DP uptake, was only 1 order of magnitude more potent than the tricyclic antidepressants. Trazadone, a claimed ant,idepressant was ten fold less effective in inhibiting DP uptake. The inhibitory potencies of PT and IP in striatal synaptosomes from rats that had been treated with reserpine did not differ from that in a nonreserpinized animal. Kinetic constants obtained from Lineweaver-Burk plots in both areas revealed no alteration in Km for transport and a decrease in Vmax by both CL and IP, indicating a noncompetitive inhibition. It was suggested that DP uptake inhibition may play some role in the action of tricyclic drugs, for example, activation of schizophrenic psychopathology, but that this action cannot be solely responsible for their antidepressant properties. 13 references.

003147 Fuller, Ray W.; Baker, John C.; Molloy, Bryan B. Lilly Research Laboratories, Division of Eli Lilly and Company, Indianapolis, IN 46206 **Biological disposition of rigid analogs of amphetamine.** Journal of Pharmaceutical Sciences. 66(2):271-272, 1977.

Several pharmacokinetic parameters of amphetamine and of amphetamine analogs with a rigid conformation (2-aminoindan, 2-aminotetralin and 2-aminobenzocycloheptene), including their levels in tissues and rates of disappearance from brain, were compared in rats. All drugs were concentrated in tissues, with the largest quantity in the lungs; the next largest quantity in the kidneys; the next largest quantity in the liver, spleen, and brain; the next largest quantity in muscle; the next largest quantity in blood. All drugs disappeared from rat brain with half-lives of 1 hr to 2 hr. Iprindole pretreatment increased drug levels in brain and prolonged the half-lives twofold to threefold. It is suggested that the biological disposition of the rigid analogs resembles generally that of amphetamine and that all of the drugs are probably metabolized by ring hydroxylation in the rat. 9 references. (Author abstract modified)

003148 Fuller, Ray W.; Roush, Betty W. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206 **Procaine hydrochloride as a monoamine oxidase inhibitor: implications for geriatric therapy.** Journal of the American Geriatrics Society. 25(2):90-93, 1977.

A series of in vitro and in vivo investigations with rats were undertaken to further evaluate procaine hydrochloride as a monoamine oxidase (MAO) inhibitor. In vitro experiments showed that inhibition by procaine hydrochloride of MAO from either rat brain or liver was substrate dependent. Procaine was more effective in inhibiting serotonin oxidation than phenylethylamine oxidation and had an intermediate effect on tryptamine oxidation. MAO activity in tissue homogenates from rats treated with procaine (150mg/kg) was inhibited most in liver, less in heart, and only very slightly in brain for a duration of up to 8 hours. Procaine injected in that dose did not alter brain norepinephrine levels and elevated only slightly the brain serotonin levels. It did not protect against the degradation of exogenous radioactive tryptamine in brain. These data confirm and extend prior observations on in vitro inhibition of MAO by procaine and suggest that in high doses procaine may inhibit MAO weakly in vivo. If the reported usefulness of procaine preparations in treating geriatric patients indeed depends upon MAO inhibition, more effective inhibitors would seem to be available. 19 references. (Author abstract modified)

003149 Gaitonde, B. B.; Joglekar, S. N. Haffkine Institute, Parel, Bombay-400 012, India **Mechanism of neurotoxicity of cardiotonic glycosides.** British Journal of Pharmacology (London). 59(2):223-229, 1977.

The mechanism by which cardiac glycosides induce neurotoxicity was investigated in cats. Pretreatment with reserpine, tetrabenazine, 2-bromolysergic acid diethylamide or parachlorophenylalanine (PCPA) suppressed the neurotoxicity induced intracerebroventricular administration of peruvoside or ouabain. Lithium carbonate and haloperidol were ineffective in suppressing the neurotoxic effects. Perfusion of the lateral ventricles of cats with peruvoside or ouabain produced a dose related release of 5-hydroxytryptamine (5-HT). Prior administration of PCPA suppressed the release of 5-HT. It is suggested that 5-HT is involved in the genesis of neurotoxicity induced by peruvoside or ouabain. 26 references. (Author abstract modified)

003150 Garland, W. A. Department of Biochemstry and Drug Metabolism, Hoffmann-La Roche Inc., Nutley, NJ 07110 **Quantitative determination of amitriptyline and its principal metabolite, nortriptyline, by GLC-chemical ionization mass spectrometry.** Journal of Pharmaceutical Sciences. 66(1):77-81, 1977.

A quantitative GLC/mass spectrometry assay for the determination of amitriptyline and its desmethyl metabolite nortriptyline in human plasma is described. Analyses of plasma samples from three subjects receiving 50mg of amitriptyline orally three times daily gave an average plasma concentration of 115ng/ml for amitriptyline and 109ng/ml for nortriptyline. Similar analyses of the plasma of three subjects who had received a single 50mg oral dose of amitriptyline showed an average maximum plasma concentration of 25ng/ml for amitriptyline and 10ng/ml for nortriptyline. The average plasma amitriptyline level was 3ng/ml and the average plasma nortriptyline level was 3ng/ml at 72 hr after administration. 18 references. (Author abstract modified)

003151 Gascon, Andre L. Departement de pharmacologie, Faculte de medecine, Universite de Montreal, Montreal, Quebec, Canada **Effect of acute stress and ouabain administration on adrenal catecholamine content and cardiac function of rats pretreated with diazepam.** Canadian Journal of Physiology and Pharmacology (Ottawa). 55(1):65-71, 1977.

The effect of acute electric shock stress and ouabain administration on adrenal catecholamine content and cardiac function of rats pretreated with diazepam was studied. The experiments were carried out to determine the participation of adrenal catecholamines in the higher incidence of cardiac arrhythmias produced by acute stress or ouabain injections in diazepam treated animals. The pretreatments of rats with diazepam (150mg/kg-1 d-1) increased significantly the adrenal catecholamine content. Consequently, the application of electrical and immobilization stress released more cathecholamines from the adrenal glands of the diazepam treated rats and also produced higher incidence of ventricular extrasystoles. Furthermore, various pretreatments of rats with diazepam (5-150mg/kg-1 d-1) also led to an increase in the catecholamine content of the adrenal gland. In diazepam treated rats, the intravenous administration of ouabain produced a greater release of adrenal catecholamines as well as a greater incidence of cardiac arrhythmias. Several hypotheses are proposed to explain the elevation of adrenal catecholamines and also the higher incidence of ventricular arrhythimias. 25 references. (Author abstract modified)

003152 George, Grizelda; Mellanby, Helen; Mellanby, Jane. University of Oxford, Dept. of Experimental Psychology, Oxford OX1 3UD, England **When does inhibition of brain acetylcholinesterase cause amnesia in rats?** Brain Research (Amsterdam). 122(3):568-574, 1977.

An attempt was made to replicate the findings of Deutsch (1966, 1971, 1972) and Hamburg (1967) that inhibition of brain acetylcholinesterase by physostigmine produces amnesia of an acquired discrimination task in rats. The attempt was unsuccessful. It was determined that the rats were learning and remembering the task with at least 40% inhibition of brain acetylcholinesterase. It is suggested that there are factors other than the age of the memory which determine what effect the inhibition of brain acetycholinesterase will have on the performance of a previously learned task. 13 references.

003153 Gerald, Michael C,; Gupta, Tribhuwan K. Division of Pharmacology, College of Pharmacy, Ohio State University, Columbus, OH 43210 **Catecholaminergic involvement in the effects of amphetamine isomers on seizure susceptibility.** European Journal of Pharmacology (Amsterdam). 41(2):231-234, 1977.

The (plus)-amphetamine isomer increase in pentylenetetrazol seizure was abolished by pretreatment with reserpine, alpha-methyltyrosine methylester (alpha-MT), FLA-63 or 6-hydroxydopa. All treatments except reserpine were found to antagonize the increase in seizure threshold produced by (minus)-amphetamine isomer. Only reserpine plus alpha-MT antagonized the decreased in seizure threshold produced by the (plus)-amphetamine ata high dose. These results indicate that amphetamine alterations in pentylenetetrazol seizure susceptibility are mediated indirectly via the release of newly synthetized and/or granular stores of catecholamines. 8 references. (Author abstract modified)

003154 Gold, B. I.; Roth, R. H. Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06510 **Kinetics of in vivo conversion of gamma-(3H)aminobutyric acid to gamma-(3H)hydroxybutyric acid by rat brain.** Journal of Neurochemistry (Oxford). 28(5):1069-1073, 1977.

Kinetics of the in vivo conversion of gamma-3H-aminobutyric acid (GABA) to gamma-3H-hydroxybutyric acid (GHB) were studied in rat brain. Radioactivity recovered as GHB was maximal 30 sec after intraventricular GABA administration and declined exponentially thereafter. From a linear transformation of the disappearance with time of GHB formed from GABA, the fractional rate of disappearance and turnover time of GHB were calculated. Pretreatment with aminooxyacetic acid reduced GHB formation, measured 4 min after GABA, to 28% of that in controls. The data strongly suggest that GABA transaminase catalyzed at least one step in the conversion pathway. GHB recoverable 4 min after GABA was unchanged when animals were pretreated with pyrazole, diphenylhydantoin, phenobarbital, ethanol, or morphine. Significantly more GHB was recovered from animals that had been pretreated with the convulsant 3-mercaptopropionic acid. 22 references. (Author abstract modified)

003155 Goldstein, Avram; Cox, Brian M.; Klee, Werner A.; Nirenberg, Marshall. Addiction Research Foundation, Palo Alto, CA 94304 **Endorphin from pituitary inhibits cyclic AMP formation in homogenates of neuroblastoma X glioma hybrid cells.** Nature (London). 265(5592):362-363, 1977.

To determine if pituitary endorphin has typical opioid effects on adenylate cyclase activity, neuroblastoma X glioma hybrid cell homogenates were injected with endorphin preparation and the resultant adenylate cyclase activity was measured. Endorphin was shown to be 100 times more potent an inhibitor of both basal and prostaglandin E stimulated formation of cyclic adenosine monophosphate than morphine. Introduction of naloxone resulted in a complete antagonism of the endorphin effect except at the highest endorphin concentrations, indicative of the expected agonist/antagonist relationships. It is suggested that the findings have physiological significance for the function of endorphins in the nervous system. 14 references.

003156 Goldstein, Howard; Harclerode, Jack; Nyquist, S. E. Department of Biology, Bucknell University, Lewisburg, PA 17837 **Effects of chronic administration of delta9-tetrahydrocannabinol and cannabidiol on rat testicular esterase isozymes.** Life Sciences. 20(6):951-954, 1977.

The effects of chronic administration of delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) on rat testicular esterase isozymes were studied using acrylamide gel electrophoretic techniques followed by staining for nonspecific esterase activity. The testicular fresh weight was reduced approximately 77% following administration of either THC or CBD for 10 days; the total body weight did not change. Band 3, an interstitial isozyme, was specifically and markedly inhibited by THC and CBD. The results suggest that THC and

CBD cause a specific depression of the testicular Leydig cell esterase isozyme, band 3. 21 references.

003157 Gordon-Weeks, Ph. University College London, Gower Street, London WC1, England **Turnover of 5-hydroxydopamine in adrenergic nerves.** Experientia (Basel). 33(2):272-274, 1977.

The turnover of 5-hydroxydopamine in guinea pig adrenergic nerves were studied. In the vas deferens the population of small granular vesicles increased from 19% in control animals to 80 to 90% 1 to 3 hours aftero administration of 5-hydroxydopamine, and gradually decreased to control values in ten days. Large granular vesicles were also loaded but the loss of enhanced granulation was more rapid than in the small granular vesicles. Treatment of the animals with reserpine before administration of 5-hydroxydopamine resulted in a much lower number of small granular vesicles (20 to 30%). 10 references. (Author abstract modified)

003158 Gordon, John H.; Shellenberger, M. Kent. Dept. of Anatomy, UCLA, Los Angeles, CA 90024 **In vitro uptake of 3-methoxytyramine by rat brain tissue slices.** Research Communications in Chemical Pathology and Pharmacology. 16(1):33-46, 1977.

One aspect of the means by which the brain handles the dopamine (DA) metabolite 3-methoxytyramine (3-MT) was examined utilizing tritiated 3-MT in synaptosomes from rat striatum and slices of both striatum and cerebellum. No accumulation of 3-MT could be demonstrated in synaptosomes, but DA uptake was inhibited by 3-MT. Studies in brain tissue slices showed: 3-MT accumulation was greater than expected from diffusion at a high concentration of amine; accumulated amine was easily washed out of tissue slices; uptake appeared to be saturable with high estimated values; and agents such as metanephrine that inhibit peripheral extraneuronal amine uptake had similar effectiveness against 3-MT uptake. It was concluded that the mechanism for accumulation of 3-MT is similar in structurally different areas of the brain, 3-MT is accumulated by a mechanism not part of the nerve terminal, and 3-MT accumulation in the brain is similar to extraneuronal accumulation of amines in the periphery. 24 references. (Author abstract modified)

003159 Graf, E.; Doppelfeld, I. S. Biologische Forschungslaboratorien, A. Nattermann u. Cie, GmbH, Nattermannallee 1, 5 Koln 30, Germany **Influence of dopamine and noradrenaline on the total cerebral blood flow of anesthetized dogs.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R33, 1977.

A study of the influence of dopamine (DA) and noradrenaline (NA) on the total cerebral blood flow (CBF) of anesthetized dogs is reported in a paper given at the 18th spring meeting of the Deutsche pharmakologische gesellschaft, held in Mainz, Germany in March 1977. In normal animals, intravenous infusions of DA and NA caused no statistically significant alterations in total CBF; however NA tended to decrease CBF and DA tended to increase CBF. There were large differences in individual reactivity to the drugs. In dogs with lowered CBF induced by bleeding, NA produced no improvement of the blood supply although it increased blood pressure and contractile force to the expected degree. In contrast, DA significantly increased CBF in a dose dependent manner without elevating the blood pressure to a similar extent. It is suggested that DA may supplement other perfusion improvement methods such as volume replacement in treating hemorrhagic shock. (Author abstract modified)

003160 Green, A. R.; Heal, D. J.; Grahame-Smith, D. G. University Department of Clinical Pharmacology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, England **Further observations on the effect of repeated electroconvulsive shock on the behavioural responses of rats produced by increases in the functional activity of brain 5-hydroxytryptamine and dopamine.** Psychopharmacology (Berlin). 52(2):195-200, 1977.

The effects of repeated electroconvulsive shock (ECS) on behavioral responses produced by increases in the functional activity of brain 5-hydroxytryptamine (5-HT) and dopamine were studied in rats. Repeated ECS resulted in enhanced hyperactivity responses to tranylcypromine and L-tryptophan, a procedure which increased brain 5-HT concentrations, or to the suggested 5-HT agonist quipazine. The enhanced responses lasted about 6 days following the last ECS. Repeated subconvulsive shocks did not produce this behavioral enhancement. Pretreatment with indomethacin before ECS did not prevent the enhanced 5-HT response suggesting that it was not the result of a rise in prostaglandin F. Repeated ECS shortened the time to loss of righting following pentobarbital but did not alter the total sleeping time. Repeated ECS enhanced locomotor activity produced by methamphetamine and circling produced by methamphetamine and apomorphine in unilateral nigrostriatal lesioned rats, suggesting an enhanced postsynaptic response. ECS did not alter the response of striatal adenylate cyclase to dopamine nor striatal adenosine-3',5'-monophosphate. The data reinforce the suggestion that electroconvulsive therapy produces increased responses to 5-HT and dopamine receptor stimulation. 22 references. (Author abstract modified)

003161 Green, Keith; Kim, Keun. Dept. of Ophthalmology, Medical College of Georgia, Augusta, GA 30902 **Acute dose response of intraocular pressure to topical and oral cannabinoids.** Proceedings of the Society for Experimental Biology and Medicine. 154(2):228-231, 1977.

The intraocular pressure (IOP) of rabbits and monkeys in response to either a single topical drop or to a single oral dose of three nitrogen containing compounds related to the cannabinoids were measured to determine their IOP lowering efficacy. One drug, with an N-propargyl substitution on the C-ring and a dimethylheptyl branched alkyl side chain, designated SP-1, was dissolved in a white, light paraffin oil. Other benzopyranopyridines, designated SP-106 and SP-204, which are both water soluble ester derivatives of SP-1 with differing side chains, were dissolved in a commerical artificial tear solution. All three drugs caused a dose dependent fall of IOP when administered either topically or orally to rabbits and monkeys. Concentrations of 0.001% to 1% applied topically and 0.3mg/kg orally were effective in rabbits. The higher concentration required in monkeys may be related to a more rapid metabolism of these compounds, thus higher dose levels of the cannabinoids would be required to produce a biological effect. 11 references.

003162 Growdon, John H. no address **Rigidity, tremor, and myoclonus in the rat immediately following injections of p-chloroamphetamine.** Neurology. 27(4):391-392, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, rats were injected with p-chloroamphetamine (PCA) in an attempt to correlate behavioral effects with lowering of brain levels of serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA). A single dose of PCA produced a stereotyped pattern of behavior that included rigid postures, tremor, and myoclonus. These effects began 5 minutes after injection and lasted 60 to 90 minutes;

their intensity was directly proportional to the amount of PCA over a 2 to 10mg/kg range. Whole brain levels of 5-HT and 5-HIAA did not differ from control values when measured 30 minutes after PCA injection, when the behavioral effects were maximal, but were significantly reduced 1 day later. Pretreatment with drugs that either interfere with the uptake of PCA into terminals of serotonergic neurons (fluoxetine), depress brain 5-HT levels (p-chlorophenylalanine), of block 5-HT receptors (methiopin or methergoline) suppressed the syndrome, whereas drugs that antagonize the effects of dopamine, norepinephrine, and acetylcholine did not. These observations implicate serotonergic mechanisms in the production of this syndrome, and provide behavioral evidence that PCA causes an immediate release of 5-HT that occurs before more permanent neurotoxic effects. (Author abstract modified)

003163 Gupta, P. K.; Gupta, R. C. Industrial Toxicology Research Centre, Mahatma Gandhi Marg, Lucknow-226001, India **Influence of endosulfan on pentobarbitone sleeping time and blood and brain concentrations in male rats.** Journal of Pharmacy and Pharmacology (London). 29(4):245-246, 1977.

The effects of endosulfan, a benzodiazepine derivative, on pentobarbitone sleeping time and blood and brain concentrations was studied in rats. The pentobarbitone induction time of rats was significantly increased and sleeping time was significantly decreased. At 30 minutes, blood and brain pentobarbitone concentrations of test animals were significantly decreased as compared to controls, while no significant changes in concentration were found in test and control animals upon awakening. Findings suggest that the inhibitory effect of endosulfan on pentobarbitone induced sleeping time may be the result of enhanced pentobarbitone metabolism rather than of increased brain sensitivity. 3 references.

003164 Gupta, T. K.; Vishnuvajjala, B. R.; Witiak, D. T.; Gerald, M. C. Division of Pharmacology, College of Pharmacy, Ohio State University, Columbus, OH 43210 **Antagonism of amphetamine stereotyped behavior by diastereoisomeric dihydrodibenzothiepin neuroleptics.** Experientia (Basel). 33(1):65, 1977.

Differences in neuroleptic activity were examined between the diastereoisomers of a dihydrodibenzothiepin derivative. No potency differences were seen between respective enantiomorphs while two of the four enantiomorphs were found to be 13.7and 8.3times more active than their respective diastereoisomers in their ability to antagonize amphetamine induced stereotyped behavior. These findings are at variance with those of Petcher, but consistent with Jilek. 9 references.

003165 Han, Wesley W.; Yakatan, Gerald J.; Maness, Dale D. Searle Laboratories, Chicago, IL 60680 **Kinetics and mechanisms of hydrolysis of 1,4-benzodiazepines II: oxazepam and diazepam.** Journal of Pharmaceutical Sciences. 66(4):573-577, 1977.

The hydrolysis kinetics of oxazepam and diazepam leading to a benzophenone product and a glycine derivative were quantified from pH1 to pH11. For oxazepam, two intermediates were isolated and identified, indicating a parallel consecutive reaction mechanism. The hydrolysis occurred uncatalyzed and demonstrated acid base catalysis for both reaction steps. One intermediate was observed by TLC for diazepam hydrolysis. This intermediate, resulting from breakage of the azomethine linkage, was different than the major intermediate isolated for oxazepam hydrolytic degradation (amide hydrolysis preferred). Stability parameters involving rate constant temperature dependence are reported. 4 references. (Author abstract)

003166 Handley, Sheila L.; Miskin, Ruth C. Pharmacology Laboratories, Dept. of Pharmacy, University of Aston, Birmingham B4 7ET, England **The interaction of some kynurenine pathway metabolites with 5-hydroxytryptophan and 5-hydroxytryptamine.** Psychopharmacology (Berlin). 51(3):305-309, 1977.

The kynurenine pathway metabolites kynurenine, 3-hydroxykynurenine, and xanthurenic acid were tested, in a dose range of 0.5mg/kg to 5.0mg/kg, against 5-hydroxytryptamine (5-HT) and 5-hydroxytryptophan (5-HTP) induced head twitches in the mouse in a dose range of 0.5to 5.0mg/kg. Kynurenine and 3-hydroxykynurenine were highly active. Low doses caused marked potentiation of the twitch response to both 5-HT and 5-HTP with increased toxicity of 5-HT. High doses caused antagonism of both responses. Xanthurenic acid was inactive over the same dose range. The effects of kynurenine could not be duplicated in the guinea-pig ileum. The relevance of these results to the involvement of kynurenine pathway metabolites in depressive illness is discussed. 19 references. (Author abstract)

003167 Hartmann, Ernest; Keller-Teschke, Marita. Boston State Hospital, Boston, MA 02124 **Biology of schizophrenia: mental effects of dopamine-beta-hydroxylase inhibition in normal men.** Lancet (London). No.8001:37-38, 1977.

In a letter to the editor the hypothesis that a biological deficit in schizophrenics involves a block of the dopamine-beta-hydroxylase (DBH) step is investigated. It was predicted that temporary DBH inhibition combined with levodopa would produce mental changes in normal subjects. The results showed that a dose of fusaric acid followed by a dose of levodopa produced definite changes and resulted in abnormal mental conditions. It is concluded that definite brief mental changes are produced in normal subjects by a DBH inhibitor plus levodopa and that these changes are reminiscent of changes frequently found in schizophrenics. 9 references.

003168 Hattori, T.; McGeer, P. L. Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, Vancouver, B.C. V6T 1W5, Canada **Electron microscopic autoradiography on Delta 8-(3H) tetrahydrocannabinol localization in brain tissue.** Toxicology and Applied Pharmacology. 39(2):307-311, 1977.

Electron microscopic studies were done on the localization of Delta8-(3H) tetrahydrocannabinol in the central gray of adult rats and the occipital cortex of young rats. Terminal boutons were the only structure showing preferential labeling in both instances. There was more labeling of cell soma in the young than in the old rats and the label was usually near the Golgi apparatus and Nissl bodies. This latter observation may correlate with the inhibition of protein and nucleic acid synthesis observed with tetrahydrocannabinol in young rats. 8 references. (Author abstract)

003169 Havemann, U. Abt. Biochemische Pharmakologie, Max Planck Institut fur experimentelle Medizin, Hermann Rein Str. 3, D-34 Gottingen, Germany **In vitro effects of opiates on cyclic AMP in rat striatal tissue.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R52, 1977.

A study of the invitro effects of opiates on cyclic adenosine monophosphate (cAMP) in rat striatal tissue is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. In homogenized corpora striata, morphine slightly but significantly lowered the concentration of cAMP. This effect

was antagonized by equimolar concentrations of naloxone. Morphine did not affect the activation of the adenylate cyclase by sodium fluoride, nor was there any alteration in tissue obtained from morphine withdrawn rats. In striatal tissue slices, morphine and leverphanol, but not dextrosphan, lowered the concentration of cAMP. The effect of morphine in tissue slices was also antagonized by naloxone. Tissue slices obtained from morphine withdrawn rats did not show any alteration in cAMP. It is concluded that the effects of opiates on cAMP cannot be the consequence of an inhibition of neurotransmitter (especially dopamine, DA) release, because considerably lower concentrations of morphine are effective in decreasing cAMP than are necessary to inhibit DA release. It is also suggested that in the experiments using homogenates, nerve endings were probably lysed osmotically. 1 reference. (Author abstract modified)

003170 Haycock, John W.; Levy, William B.; Cotman, Carl W. Department of Psychobiology, University of California, Irvine, CA 92717 **Pentobarbital depression of stimulus-secretion coupling in brain -- selective inhibition of depolarization-induced calcium-dependen release.** Biochemical Pharmacology (Oxford). 26(2):159-161, 1977.

The effects of pentobarbital (PB) upon calcium (Ca) dependent secretion of norepinephrine (NE) and gamma aminobutyric acid (GABA), two presumably inhibitory transmitters in the brain, were studied from synaptosomes isolated in the mouse brain. The results of the experiments indicate that PB inhibits the depolarization triggered secretion of accumulated neurotransmitters from the brain at PB concentrations within anesthetic ranges. The depression of release by PB was restricted to a situation in which depolarizing agents were used to facilitate Ca influx, delimiting a selective locus of action for this PB effect. The ability of PB to affect the coupling of Ca to release specifically by depolarizing agents could result from a selective PB effect on membrane fluidity or surface charge at specialized regions of the presynaptic membrane. These findings suggest that investigations of PB effects at the level of such Ca ionophores may be useful for further distinguishing molecular mechanisms contributing to PB action. 36 references.

003171 Herting, T.; Erbler, H. C. Institut fur Pharmakologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, D-3000 Hannover 61, Germany **Effect of lithium on the time course of plasma levels of ACTH, corticosterone, aldosterone, and on plasma renin activity in rats.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R41, 1977.

A study of the effect of lithium on the time course of plasma levels of adrenocorticotropic hormone (ACTH), corticosterone, aldosterone, and on plasma renin activity in rats is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. Lithium produced large increases in plasma ACTH levels, corticosterone levels, and aldosterone levels as well as in plasma renin activity. It is posited that the increase in corticosteroid secretion following lithium administration is due to stimulation of ACTH secretation as well as to the known direct effects of lithium on the adrenal cortex, and that stimulation of aldosterone secretion is also subject to more complex mechanisms including those mediated by the renin/angiotensin system. (Author abstract modified)

003172 Hine, Bromfield; Gershon, Samuel. Dept. of Psychiatry, New York Univ. School of Medicine, 550 1st Avenue, New York, NY 10016 **Haloperidol attenuation of morphine abstinence: synergistic effect of acute lithium administration.** Journal of Pharmacy and Pharmacology (London). 29(4):238-240, 1977.

The effects of acute lithium (Li) and haloperidol administration on the attenuation of morphine abstinence in rats was studied in three experiments. Experiments 1 and 2 attempted to determine the effects of acute Li and haloperidol, alone or in combination on morphine abstinence scores. In Exp. 1, doses of Li did not significantly modify abstinence scores while in Exp. 2, doses of Li and haloperidol demonstrated a clearly synergistic effect of Li on an otherwise subthreshold abstinence modifying dose of haloperidol. This effect of Li was still discernible even with the marked suppression of abstinence produced by haloperidol alone. In Exp. 3, in which Li was replaced by alpha-methyltyrosine (alpha-MT) alpha-MT plus haloperidol was no more effective than haloperidol alone in attenuating abstinence. It is concluded that the data demonstrate a synergistic effect of Li on haloperidol attenuation of morphine abstinence that is probably not due to alpha-MT-like effects of Li on catecholamine synthesis. 23 references.

003173 Hine, Bromfield; Torrelio, Marina; Gershon, Samuel. Neuropsychopharmacology Research Unit, Department of Psychiatry, New York University School of Medicine, 550 First Ave., New York, NY 10016 **Analgesic, heart rate, and temperature effects of delta8THC during acute and chronic administration to conscious rats.** Pharmacology (Basel). 15(1):65-72, 1977.

Acute and chronic effects of delta8-tetrahydrocannabinol (THC) on tail flick, heartrate, and rectal temperature responses in conscious, unrestrained male rats were studied. In the acute experiment, unidirectional, dose dependent analgesic, hypothermic, and negative chronotropic cardiac effects were observed within the dose range employed. Of the three variables, heartrate decreases were most sensitive to the effects of THC, reaching significance at 2mg/kg. Rapid development of tolerance occurred for all three measures, with complete tolerance developing within 13 days only to the heartrate decrease. 29 references. (Author abstract modified)

003174 Hockel, S.; Muller, W. E; Wollert, U. Pharmakologisches Institut der Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, Germany **Influence of diazepam and imipramine on the uptake of tryptophan in slices of different parts of the rat brain.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R56, 1977.

A study of the influence of diazepam and imipramine on the uptake of radiolabeled tryptophan in tissue slices of different parts of the rat brain is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. Diazepam singificantly increased tryptophan uptake in midbrain, hypothalamus, striatum, hippocampus, cerebellum, and cortex, but not in the medulla oblongata. Impramine decreased tryptophan uptake into the hippocampus but not into the other tissues studied. (Author abstract modified)

003175 Hoffmeister, Friedrich. Institut fur Pharmakologie der BAYER AG, Wuppertal-Elberfeld, Germany **Self-administration of codeine plus acetylsalicylic acid in rhesus monkeys with unlimited access to the drugs.** Pharmacology Biochemistry and Behavior. 6(2):179-182, 1977.

Self-administration of codeine plus acetylsalicylic acid (ASA) was studied in 12 rhesus monkeys with unlimited access to the drugs and the reinforcing effects of each drug and their combination were examined. Responding was engendered and maintained by infusions of codeine. Infusions of ASA failed to initiate and maintain responding during a 14 day drug period, but a combination of ASA and codeine initiated responding beginning on the ninth or tenth day. Monkeys self-administered codeine without signs of intoxication, but the monkeys self-administering the combination of drugs died, exhibiting signs of severe intoxication. A combination of codeine with a larger dose of ASA was not self-administered until day 12; only two of the three monkeys began self-administration, and those two died of intoxication. Experiments suggest that even toxic doses of ASA will not prevent monkeys from self-administration when offered together with a reinforcing drug such as codeine under a schedule of continuous self-administration. 5 references. (Author abstract modified)

003176 Huang, J. T.; Wajda, I. J. New York State Research Institute for Neurochemistry and Drug Addiction, Ward's Island, New York, NY 10035 **The influence of 3,4-dihydroxyphenylacetic acid on the accumulation of 5-hydroxyindoleacetic acid in the choroid plexus and kidney cortex slices of rats.** Research Communications in Chemical Pathology and Pharmacology. 16(4):649-668, 1977.

An experimental study is made of the stimulation of transport of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, by 3,4-dihydroxyphenylacetic acid (DOPAC), a dopamine metabolite. In vitro, the choroid plexus of rats accumulates 5-HIAA by active transport. The kidney cortex slices also showed active accumulation of this organic acid, which proved to be inhibited by most of the organic acids tested. In the choroid plexus DOPAC stimulated the accumulation of 5-HIAA, whereas in the kidney slices DOPAC was inhibitory. This stimulating effect of DOPAC was blocked by homovanillic acid and probenecid. Metabolic inhibitors such as 2,4-dinitrophenol and N-ethylmaleimide also blocked the stimulation, but sodium fluoride was ineffective. Omission of calcium, but not magnesium ion in the incubation medium depressed the accumulation of 5-HIAA. DOPAC still produced the stimulating action in calcium free medium. The release of 5-HIAA from choroid plexus was retarded by DOPAC. These results suggest that the stimulating action of DOPAC may be due to a calcium dependent active transport system and delay of 5-HIAA release. 14 references. (Author abstract modified)

003177 Hunt, Walter A.; Redos, James D.; Dalton, Thomas K.; Catravas, George N. Behavioral Sciences Department, Armed Forces Radiobiology Research Institute, Bethesda, MD 20014 **Alterations in brain cyclic guanosine 3′:5′-monophosphate levels after acute and chronic treatment with ethanol.** Journal of Pharmacology and Experimental Therapeutics. 201(1):103-109, 1977.

The effects of acute and chronic ethanol treatment on cyclic guanosine 3′,5′-monophosphate (cGMP) levels were studied in six areas of the rat brain. Rats were either gavaged with a single dose of ethanol (6 g/kg) or rendered ethanol dependent with 11 to 15g/kg/day in 3 to 5 fractions over a 4 day period. A single dose of ethanol depleted cGMP levels in only five areas of the brain studied. In the two areas in which a time course of the response was determined, the caudate nucleus and cerebral cortex, cGMP depletion was maximal 1 hour after ethanol administration when blood ethanol concentrations were highest. The cGMP levels returned to control values as blood ethanol was eliminated. In ethanol dependent animals still intoxicated, cGMP was reduced but not to the same magnitude in the cerebellum and brainstem when compared with the response obtained after a single dose at equivalent blood ethanol concentrations. During the ethanol withdrawal syndrome cGMP levels had returned to control values. The data suggest that cGMP depletion may play a role in ethanol induced intoxication and that tolerance to this effect develops concurrently with behavioral tolerance. 54 references. (Journal abstract modified)

003178 Hyttel, John. Department of Pharmacology and Toxicology, H. Lundbeck & Co. A/S, Ottiliavej 7-9, DK-2500 Copenhagen-Valby, Denmark **Changes in dopamine synthesis rate in the supersensitivity phase after treatment with a single dose of neuroleptics.** Psychopharmacology (Berlin). 51(2):205-207, 1977.

The effects of cis (Z)flupenthixol, fluphenazine and haloperidol on the accumulation of radiolabeled dopamine (DA) formed from radiolabeled tyrosine were studied in mice. The neuroleptics all changed DA synthesis rate in the same way, initially causing an increase which was followed by a decrease after approximately 3 days. The results were compared with the findings of Christensen. A very close correlation between receptor blockade and increase in DA synthesis and between receptor supersensitivity and decrease in DA synthesis was found. It is suggested that the changes in DA receptor activity are followed by compensatory changes in DA synthesis rate. 8 references. (Author abstract modified)

003179 Hyttel, John. Department of Pharmacology and Toxicology, H. Lundbeck & Co. A/S, Ottiliavej 7-9, DK-2500 Valby, Denmark **Effect of a selective 5-HT uptake inhibitor--Lu 10-171--on rat brain 5-HT turnover.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(3):439-446, 1977.

The effect of a selective serotonin (5-HT) uptake inhibitor, 1-13-(dimethylamino)propyl)-1-p-fluorophenyl)-5-phthalancarbonitrile (Lu 10-171), citalopram, on rat brain 5-HT turnover was studied. After a single dose of Lu 10-171 the concentration of 5-hydroxyindoleacetic acid (5-HIAA) was reduced from 1-24 hr after treatment, whereas that of 5-HT was practically unchanged, indicating decreased turnover of 5-HT in the brain. The rate of 5-HIAA accumulation in the brain after probenecid was reduced after Lu 10-171. Treatment with Lu 10-171 led to a decreased fall in 5-HT and increased fall in 5-HIAA after inhibiton of 5-HT synthesis with parachlorophenylalanine. Unexpectedly Lu 10-171 did not change either the accumulation of 5-HT or the decrease in 5-HIAA after inhibition of monoamine oxidase with pargyline. The results are generally consistent with the proposed negative feedback regulation of 5-HT neuronal firing rate due to the abundance of 5-HT at postsynaptic receptors after inhibition of the reuptake mechanism. 14 references. (Author abstract modified)

003180 Iversen, Leslie. no address **Anti-anxiety receptors in the brain?** Nature (London). 266(5604):678, 1977.

A review of the literature concerning the mode of action of the benozdiazepines, a widely used group of psychotropic drugs, shows the latest hypothesis to be that of a saturable high affinity binding mechanism at specific sites. It is noted that the highest density of 3H-diazepam binding sites were found in the frontal and occipital cortex of rat brain, areas not known to be enriched in any of the known transmitter substances. Further research could possibly lead to the discovery of a naturally occurring ligand for benzodiazepine receptors. 7 references.

003181 Izquierdo, I.; Schutz, R.; Prado de Carvalho, L. Departamento de Fisiologia, Escola Paulista de Medicina, Rua Botucatu, 862 04023 Sao Paulo, SP., Brazil **The effect of apomorphine and haloperidol on the RNA content of brain structures of the rat.** Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 224(2):258-262, 1977.

A study of the effect of apomorphine and haloperidol on the RNA content of brain structure of the rat is presented. At a dose of 0.5mg/kg, apomorphine caused an increase of the RNA content of the septal nucleus of rats (n. medialis + n. lateralis + n. accumbens); after 2.5mg/kg this effect became more marked and, in addition, there was an increase of RNA in the caudate nucleus. All effects were antagonized by 0.5mg/kg of haloperidol. These data suggest that apomorphine acts, at different dose levels, on different sites of the brain. This might be related to the also different behavioral effects of apomorphine at those two dose levels. Haloperidol on its own caused a fall of RNA in the amygdaloid nucleus which was not counteracted by either of the two doses of apomorphine. Neither drug had an influence on hypothalamic RNA concentration. 24 references. (Journal abstract modified)

003182 Jandhyala, B. S.; Buckley, J. P. Division of Cardiovascular Research, University of Houston, Houston, TX 77004 **Autonomic and cardiovascular effects of chronic delta9-tetrahydrocannabinol administration in mongrel dogs.** Research Communications in Chemical Pathology and Pharmacology. 16(4):593-607, 1977.

To study the autonomic and cardiovascular effects of chronic delta9-tetrahydrocannabinol (delta9-THC), the drug was administered to mongrel dogs in doses of 1mg/kg, twice a day for 7 days. Chronic administration of delta9-THC failed to produce any major changes in the pulmonary or systemic hemodynamics in the myocardial contractility, or any significant alterations either in the transmission in the lumbar sympathetic chain or in the activity of autonomic receptors within the cardiovascular system of mongrel dogs. Further systemic pressor responses to bilateral carotid occlusion and reflexly mediated alterations in the perfused hindlimb vascular resistance were essentially identical in both the treated and placebo groups. Pressure flow curves obtained from the perfused hindlimb preparations suggested that in contrast to the acute studies, neurogenic tone to the hindlimb vasculature was unaltered by chronic delta9-THC and intrinsic tone of the vascular smooth muscle was significantly depressed in the treated animals; in addition, it appears that the tone due to circulating catecholamines was significantly enhanced in treated animals. Although several acute cardiovascular and autonomic effects of delta9-THC may not be evident following chronic THC treatment, prolonged use may demonstrate certain new pharmacological properties and/or mechanism of actions which cannot readily be seen in the acute studies. 16 references. (Author abstract modified)

003183 Jandhyala, Bhagavan S.; Steenberg, Marie L.; Perel, James M.; Manian, Albert A.; Buckley, Joseph P. Cardiovascular Research, Dept. of Pharmacology, University of Houston, Houston, TX 77004 **Effects of several tricyclic antidepressants on the hemodynamics and myocardial contractility of the anesthetized dogs.** European Journal of Pharmacology (Amsterdam). 42(4):403-410, 1977.

To evaluate comparatively the effects of imipramine and several of its metabolites, and 3-C-imipramine and its metabolite 3-Cl-8-OH-imipramine on myocardial contractility, imipramine analogs were intravenously administered to anesthetized mongrel dogs. Significant reduction in the cardia output produced by lower doses (2.5mg/kg) of imipramine and (2-OH-DMI) was not due to a depression of myocardial contractility. In contrast, 2-OH-imipramine (1.25mg/kg) and desmethylimipromine (DMI) (2.5mg/kg) significantly reduced contractility within 10 min after administration; however, significant decrease in the cardiac output did not occur until after 60 min. Higher doses (5mg/kg) of imipramine, DMI and 2-OH-DMI significantly attenuated cardiac rate, contractility and output within 5 min after administration. 2-OH-imipramine, 2.5mg/kg, depressed contractility and cardiac output to a degree equivalent to that produced by 5mg/kg of imipramine, DMI and 2-OH-DMI. 3-Chloro-imipramine (5mg/kg) induced decrease in the cardiac output was essentially due to a significant reduction in the heartrate since the effects of this compound on the contractility were transient in nature. 3-Cl-8-OH-metabolite of this compound had no significant effects on the cardiovascular system. The results demonstrated that the complex cardiovascular effects of tricyclic antidepressants observed in these studies were perhaps due to a direct and/or autonomically mediated effects on the heart and vasculature. Further, the data support the conclusions that the activity of the parent compounds together with that of the metabolites contributes to overall changes observed. While all the agents are capable of reducing cardiac output, 2-OH-metabolite of imipramine appears to be most toxic on the myocardium and 3-Cl-imipramine possessed only transient effects on the contractile properties. 29 references. (Author abstract)

003184 Jonsson, John. Psychiatric Research Center, Ulleraker Hospital, University of Uppsala, S-75017 Uppsala, Sweden **On the aromatic hydroxylation of amphetamine in rat liver microsomes and perfused liver preparations: effects of long-term administration.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(4):517-528, 1977.

The aromatic hydroxylation of amphetamine in rat liver microsomes and perfused liver preparations was studied and the effect of chronic administration of amphetamine on the microsomal and perfused liver metabolism of the central stimulant was investigated. Liver microsomal p-hydroxylation of amphetamine to parahydroxamphetamine (pOHA) was dependent on the NADP and was inhibited by carbon monoxide, indicating the involvement of cytochrome P-450. SKF 525-A, fenfluramine and desemthylimipramine were the most effective inhibitors of this pathway of amphetamine metabolism. Repeated administration of pheonbarbital resulted in reduced p-hydroxylation of amphetamine in vitro. Chronic administration of amphetamine reduced the microsomal p-hydroxylation of amphetamine without apparent changes in the cytochrome P-450 levels or in the activity of NADPH-cytochrome c reductase. The aromatic hydroxylation of aniline and the demethylation of ethylmorphine was not affected by this treatment. However, the 455 nm complex formed during the microsomal metabolism of N-hydroxyamphetamine was increased by the long-term administration of amphetamine. Results indicate some pecularities of the in vitro hydroxylation of amphetamine by rat liver microsomes. Amphetamine disappeared from the perfusate of the perfused liver at the same rate in rats given a single dose of amphetamine and in rats given amphetamine orally for four weeks. The excretion of pOHA and its conjugate increased at 60 and 90 min. and 30, 60, and 90 min.,respectively, in the perfusate of the same experiment as compared to the controls. The total excretion of radioactive amphetamine metabolites at the end of the perfusion was increased in the perfusate and reduced in the bile compared to the control experiments. 35 references. (Author abstract modified)

003185 Jorgensen, Karin Damm. Department of Pharmacology, Novo Industri A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark **Actions of fenfluramine on glucose uptake in vitro and in vivo.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(3):401-417, 1977.

The effects of fenfluramine (FEN) on glucose uptake were studied in vitro and in vivo in normal and diabetic rats and dogs. FEN stimulated glucose uptake of the isolated hemidiaphragm from normal and streptozotocin diabetic rats in the presence of insulin, but did not cause an increased storage of glycogen. During hind leg perfusion of the dog FEN stimulated peripheral glucose uptake, but not lactate or free fatty acid release. FEN caused an improvement of glucose tolerance in normal glucose primed rats. A single dose of FEN lowered the blood glucose levels in streptozotocin diabetic rats and in diabetic dogs treated with insulin. Prolonged treatment with FEN of streptozotocin diabetic rats did not affect blood glucose levels. Additional treatment for 1 week of insulin dependent diabetic dogs with small nonanorexic doses of FEN resulted in slightly decreased blood glucose levels. The dog could not be maintained on FEN without insulin. The results indicate that the lowering effect of FEN on blood glucose is due to an increased uptake of glucose by the tissues and is synergistic with insulin and that glucose is probably oxidized to carbon dioxide. FEN can probably diminish the insulin requirements in diabetic animals in which some anorexic effect is likely to occur. 12 references. (Author abstract modified)

003186 Jori, Armanda; Dolfini, Enzo. Istituto de Richerche Farmacologiche Mario Negri, Via Eritrea 62, I-20157 Milan, Italy **Tolerance to the increase of striatal homovanillic acid elicited by several anorectic drugs.** European Journal of Pharmacology (Amsterdam). 41(4):443-445, 1977.

An investigation to determine whether tolerance to the increase in striatal homovanillic acid (HVA) levels induced by several anorectic drugs develops, and whether cross-tolerance with amphetamine occurs, was conducted. Tolerance to the HVA increase occurred with levoamphetamine, dextroamphetamine, and mazindol. The effects of fenfluramine and trifluoromethylphenyl(benzoyloxy)ethylamino-2-propane (S-992) on striatal HVA levels were not reduced by subchronic treatments. Cross-tolerance to this effect developed between amphetamine and mazindol, but pretreatment with fenfluramine or S-992 did not induce cross-tolerance to amphetamine. 9 references. (Author abstract modified)

003187 Juorio, A. V. Psychiatric Research Division, University Hospital, Saskatoon, Saskatchewan S7N OW8, Canada **Effects of D-amphetamine and antipsychotic drug administration on striatal tyramine levels in the mouse.** Brain Research (Amsterdam). 126(1):181-184, 1977.

The effects of D-amphetamine (AM) and the antispychotic drugs, chlorpromazine (CZ) and haloperidol (HA) on striatal tyramine levels were studied in mice. AM, CZ, and HA significantly decreased p-tyramine (pT) in the striatum, but did not affect the m-tyramine (mT) level. When mice were pretreated with either CZ or HA before injection with AM, the pT striatum levels were reduced in comparison with that obtained after each drug was administered by itself. Striatal mT was increased 53 and 177% after the administration of CZ and HA, respectively, before injection of AM. The pT/mT ratio was reduced after the administration of either antipsychotic drug or AM and was further reduced by the drugs in association. The results indicate that the drugs alone or in combination either reduce the synthesis of pT or interfere with the neuronal uptake and/or storage of pT thus exposing it to increased oxidation by monoamine oxidase. The increased levels of mT may be the result of the formation of mT by dehydroxylation of dopamine or its precursor. 20 references.

003188 Kaakkola, Seppo; Ahtee, Liisa. Dept. of Pharmacology, University of Helsinki, Siltavuorenpenger 10, SF-00170 Helsinki 17, Finland **Effect of muscarinic cholinergic drugs on morphine-induced catalepsy, antinociception and changes in brain dopamine metabolism.** Psychopharmacology (Berlin). 52(1):7-15, 1977.

The effects of drugs acting on muscarinic cholinergic receptors on the catalepsy, antinociception and changes in rectal temperature and in brain dopamine (DA) metabolism induced by morphine were studied in Wistar rats. Scopolamine was about three times as potent as atropine in potentiating the cataleptic effect of morphine. Methylscopolamine and methylatropine did not alter the cataleptic effect of morphine. Pilocarpine and arecoline slightly but significantly antagonized and spiro-(N'-methylpiperidyl-4')-N-ethylsuccinimide (RS86) clearly antagonized the morphine catalepsy. RS86 antagonized the atropine induced potentiation of morphine catalepsy. The antinociceptive effect of pilocarpine was additive and that of RS86 less than additive with morphine. The antimuscarinic compounds did not alter the antinociceptive effect of morphine. The antimuscarinic drugs reduced the concentration of striatal homovanillic acid (HVA) in about same proportion in control and morphine treated rats. Both the muscarinic compounds and morphine increased the concentration of striatal HVA, but when combined their effects were not significantly different from those of morphine alone. Scopolamine antagonized and and pilocarpine accelerated the morphine induced increase in the rate of depletion of cerebral DA content. It is suggested that the effects of muscarinic and antimuscarinic cholinergic drugs on the cataleptic effect of morphine are opposite to their effects on the catalepsy induced by neuroleptic compounds. 53 references. (Author abstract modified)

003189 Kaariainen, Ilpo. Department of Pharmacology, University of Helsinki, Siltavuorenpenger 10, SF-00170 Helsinki 17, Finland **Effects of GABAergic drugs on the catalepsy, striatal homovanillic acid increase and antinociception caused by pilocarpine in rats.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(1):188-192, 1977.

The effects of aminooxyacetic acid (AOAA), which increases the cerebral concentration of gamma-aminobutyric acid (GABA), and baclofen, a structural analogue of GABA, on the catalepsy, the striatal homovanillic acid (HVA) increase, and/or the antinociception caused by pilocarpine are examined. Pilocarpine induced catalepsy within 20 minutes after administration; neither AOAA nor baclofen caused catalepsy. Pretreatment with AOAA or baclofen had no effect on the pilocarpine induced catalepsy. Pilocarpine increased striatal homovanillic acid (HVA). Baclofen, but not AOAA, increased HVA slightly but significantly. Pretreatment with AOAA or baclofen did not change the pilocarpine induced HVA increase. Pilocarpine increased the jump threshold in animals receiving electric footshocks. AOAA and baclofen did not change the jump threshold values significantly. Pretreatment with baclofen (but not AOAA) increased slightly the antinociceptive effect of 25mg/kg of pilocarpine but not that of 50mg/kg. It is suggested that although GABAergic neurones have an inhibitory effect on dopaminergic neurones, they do not change the effect of pilocarpine, which probably causes catalepsy by mechanisms other than by blockade of striatal dopaminergic receptors. 10 references.

003190 Kan, Jean-Paul; Pujol, Jean-Francois; Malnoe, Armand; Strolin-Benedetti, Margherita; Gouret, Claude; Raynaud, Guy. Chemistry Department, Indiana University, Bloomington, IN 47401 **Effects of a new antidepressant (3-methy) 3-phenyl 5-hydroxy methyl 2-oxazolidinone (toloxatone) upon 5-hydroxytryptamine pathways (1).** European Journal of Medicinal Chemistry (Paris). 12(1):13-16, 1977.

The effects of a new antidepressant, (3-methyl)-3-phenyl-5-hydroxymethyl-2-oxazolidinone (toloxatone) (TX) on 5-hydroxytryptamine (5-HT) pathways were studied in cats, mice and rats. TX prevented numerous effects of reserpine; it antagonized principally ponto-geniculo-occipital waves (PGO waves), ptosis, and hypothemia, but had little activity on hypomotility and catalepsy. TX decreased PGO waves induced by p-chlorophenylalanine. TX did not potentiate stereotypes induced by amphetamine or apomorphine, and did not antagonize prochlorperazine catalepsy. TX potentiated 5-hydroxytryptophan tremors, but was inactive in dopa and tryptamine tests. Its monoamine oxidase inhibitor effect was weak and of short duration. The results indicate the central nervous system activity of TX is more serotoninergic than catecholaminergic and that a short, selective and unusual inhibition of monamine oxidase might be involved. In biochemical investigation, TX increased 5-HT levels in rat brain and exerted two agonistic effects on 5-HT pathways: an activation of tryptophan hydroxylase and a reversible noncompetitive inhibition of monoamine oxidase. TX did not inhibit 5-HT uptake by rat blood platelets or brain slices and did not inhibit tryptophan pyrrolase of liver. The results on 5-HT do not rule out a possible interaction of TX with the catecholamine pathways. 29 references.

003191 Katz, Jonathan B.; Catravas, George N. Department of Neurobiology, Armed Forces Radiobiology Research Institute, Bethesda, MD 20014 **Absence of morphine antagonism of prostaglandin E1-stimulated 3H-3′,5′-cyclic adenosine monophosphate accumulation in a rat brain mince system.** Brain Research (Amsterdam). 120(2):263-268, 1977.

Prostaglandin E-1 (PGE-1) stimulated radiolabeled 3′,5′-cyclic adenosine monophosphate (cAMP) accumulation was studied in a rat brain mince system to determine if stimulation of net cAMP accumulation could be prevented or reversed by morphine. Incubated minces of whole brain minus cerebellum were prepared from naive animals, acutely morphine treated animals and morphine tolerant/withdrawing animals. Basal levels of cAMP accumulation in the three groups were equal within experimental limits. Addition of morphine to the PGE-1 stimulated minces did not prevent or reverse stimulation of cAMP accumulation in any of the experimental groups. The results suggest that PGE-1 stimulated cAMP accumulation in brain may not be the locus of opiate action in the phenomena of opiate analgesia, tolerance and dependence. 18 references. (Author abstract modified)

003192 Kauffmann, H.; Doring, C. Institute of Neuropsychopharmacology, Free University of Berlin, Ulmenallee 30, D-1000 Berlin 19, Germany **Effect of tryptoline, an unsubstituted beta-carboline, on serotonergic and dopaminergic mechanisms.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R54, 1977.

Studies of the effects of tryptoline, an unsubstituted beta-carboline, on serotonergic and dopaminergic mechanisms are reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, helf in Mainz, Germany in March 1977. Administration of tryptoline to animals produced: 1) analgesia about 10 times weaker than that produced by morphine which was blocked by serotonin (5-hydroxytryptamine, 5-HT) antagonists; 2) hypothermia; 3) reduced motility; 4) prolongation of the hexobarbital sleeping time with no effect on the elimination rate; 5) reduction of food and water consumption and bodyweight; 6) antagonism of apomorphine induced compulsive movements; 7) antagonism of the rotational behavior elicited by apomorphine after medial forebrain bundle lesions; and 8) increased susceptibility to apomorphine after withdrawal from chronic tryptoline treatment. The findings support the hypothesis of a serotonergic action of tryptoline and an antagonism of dopaminergic mechanisms. Tryptoline produced its antidopaminergic action at lower doses and the effect could be enhanced over a wider range than the stimulation of 5-HT. (Author abstract modified)

003193 Kehr, W. Dept. of Neuropsychopharmacology, Schering AG, Mullerstrasse 170-178, D-1000 Berlin 65, Germany **Effect of lisuride and other ergot derivatives on monoaminergic neurotransmission in rat brain.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R54, 1977.

A study of the effect of lisuride and other ergot derivatives on monoaminergic neurotransmission in rat brain is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. The effects of lisuride hydrogen maleate on monoamine synthesis, turnover, and receptor activity were compared with those of lysergic acid diethylamide (LSD), methysergide, yohimbine, and methiothepin. Lisuride decreased DOPA formation in the dopamine (DA) rich areas c. striatum and mesolimbic cortex. In these brain areas, lisuride antagonized the stimulation of DOPA formation induced by cerebral hemitranssection at the level of the caudal hypothalamus; haloperidol effectively antagonized this effect. The accumulation of 3-methoxytyramine (3-MT) after inhibition of monoamine oxidase was used as an indicator of DA relase. Lisuride and LSD reduced 3-MT formation, while methysergide had no effect. Lisuride increased serotonin (5-hydroxytryptamine, 5-HT) and decreased 5-hydroxyindoleacetic acid concentrations. All of the compounds tested except methiothepin reduced 5-hydroxytryptophan accumulation in whole brain. In spinal reserpinized rats lisuride was indistinguishable from LSD in inducing extension and athetoid movements of the hind legs. It is posited that the data support the hypothesis that lisuride is a direct agonist on presynaptic and postsynaptic DA and 5-HT receptors. (Author abstract modified)

003194 Keim, Kevin L.; Sigg, Ernest B. Roche Research Division, Nutley, NJ 07110 **Plasma corticosterone and brain catecholamines in stress: Effect of psychotropic drugs.** Pharmacology Biochemistry and Behavior. 6(1):79-85, 1977.

The effects of representative psychoactive drugs on restraint stress induced changes in prosencephalic norepinephrine and dopamine, and on plasma corticosterone (CS) as an index of adrenocorticotropin hormone (ACTH) secretion were examined. The possible physiological association between central catecholamines and ACTH were further elucidated. In nonstressed rats, subcutaneous administration of haloperidol (HAL) and large doses of diazepam (DZ) increased plasma corticosterone (CS). Hypothalamic norepinephrine (NE) was lowered significantly by desmethylimipramine (DMI), HAL and, to a lesser extent, by DZ and phenobarbital (PHB). In rats pretreated with either DZ, DMI, HAL, or PHB the restraint/induced rise of CS was diminished, DZ being most potent. CPZ had a variable effect, slightly increasing or decreasing the CS response. Pretreatment (16 hr) with pargyline (PA) did not affect the CS rise to stress. The reduction

of hypothalamic NE evoked by restraint was attenuated by DZ, and to a lesser extent, by PHB and HAL. Restraint of PA treated rats did not lower the PA elevated hypothalamic NE. The stress-induced increase in hypothalamic dopamine was prevented by CPZ and, partially, by PHB. It is emphasized that the net plasma CS and brain catecholamine changes in response to stress are dependent on the drug induced neuroendocrine feedback state prevalent immediately before commencement of the stress procedure. 38 references. (Journal abstract modified)

003195 Key, B. J.; Mehta, V. H. Department of Pharmacology, Medical School, University of Birmingham, Birmingham B15 2TJ, England **Changes in electrocortical activity induced by the perfusion of 5-hydroxytryptamine into the nucleus of the solitary tract.** Neuropharmacology (Oxford). 16(2):99-106, 1977.

The effects of 5-hydroxytryptamine (5-HT) and its antagonists D-lysergic acid diethylamide (LSD) and 2-bromolysergic acid diethylamide (bromo-LSD) on electrocortical activity after perfusion directly into the nucleus of the solitary tract of cats are investigated. The relationship of these changes to alterations in the responsiveness of the animal to sensory stimuli is assessed. 5-HT induced or increased the amount of electrocortical synchronization and decreased the responsiveness of the animal to auditory stimulation or to electrical stimulation of the mesencephalic reticular formation. Larger concentrations of 5-HT elicited a secondary alerting effect towards the end of the perfusion period. LSD induced alerting or produced varying degrees of electrocortical desynchronization when perfused into a sleeping animal. Prior perfusion of LSD, in a concentration which produced an increase in sensory responsiveness but only transient electrocortical desynchronization, blocked the sedative effects of a subsequent perfusion of 5-HT. In these experiments, LDS and 5-HT appeared to act additively. Bromo-LSD had no effect on electrocorticogram, sensory responsiveness, or 5-HT induced sedation. 45 references. (Author abstract modified)

003196 Kilbey, M. Marlyne; Ellinwood, Everett H., Jr. Duke University Medical Center, Box 3870, Durham, NC 27710 **Reverse tolerance to stimulant-induced abnormal behavior.** Life Sciences. 20(6):1063-1076, 1977.

Reverse tolerance to stimulant induced abnormal behavior (SIAB) was studied by measuring the changes in behavior of female rats induced by repeated, daily administrations of d-amphetamine or cocaine. SIAB refers to repetitive patterns of locomotion, rearing, sniffing, gnawing, or biting. Potentiation of stereotyped behavior in the initial postinjection period was found during and following daily treatment with both drugs, which suggests a decrease in the latency to reach maximum stereotyped behavior. Behavior induced by apomorphine was potentiated during the initial postinjection period when the rats were pretreated with a course of repeated, daily administrations of d-amphetamine or cocaine, suggesting the development of supersensitive dopaminergic postsynaptic mechanisms. 18 references.

003197 Klemm, W. R.; Dreyfus, L. R.; Forney, E.; Mayfield, M. A. Department of Biology, Texas A & M University, College Station, TX 77843 **Morphine-induced regional and dose-response differences in multiple-unit activity in rabbits.** Neuropharmacology (Oxford). 16(3):191-204, 1977.

EEG and multiple unit activity were recorded from 14 areas of the rabbit brain which had been suggested in the literature as primary target sites of opiate action. EEG recordings disclosed a dose related decrease in the incidence of theta rhythm. Subjective evaluation of tracings from all areas did not disclose any drug related regional differences. Quantitative analysis of multiple unit activity revealed only a mild positive correlation between percent time theta and change in multiple unit activity. Results in certain areas supported the hypothesis of differential responsiveness to morphine, both in terms of brain areas affected and response latency. Those brain areas where multiple unit activity responses indicated probable target sites were the cingulate cortex and hippocampus, and to a lesser extent, the anterior thalamic nucleus, medial thalamic nucleus, brainstem reticular formation, cerebral cortex, fimbria/fornix, septum, and substantia nigra. It is concluded that multiple unit activity is a sensitive index of opiate effect and that this approach is an appropriate method to identify and characterize primary sites of opiate action. 57 references. (Author abstract modified)

003198 Koyuncuoglu, H.; Genc, E.; Canberk, A.; Sagduyu, H. Department of Pharmacology, Istanbul Medical Faculty Capa, Istanbul, Turkey **Mutual effects of morphine and aspartic acid on brain levels in mice.** Psychopharmacology (Berlin). 52(2):181-184, 1977.

The mutual effects of morphine and aspartic acid on brain levels in mice were studied. One group of mice were given tritiated aspartic acid and another group was given tritiated aspartic acid and aspartic acid (30mg/kg). Half of each group were injected with morphine simultaneously. Morphine increased the brain levels of labeled aspartic acid, while the brain content of morphine was decreased by the additional aspartic acid. It was thought that the results might be related to a heteroexchange existing between the morphine content in the central nervous system and aspartic acid in the circulation. In addition aspartic acid can possibly stimulate or inhibit the efflux or influx of morphine in the central nervous system. 19 references. (Author abstract modified)

003199 Krivoy, William A.; Kroeger, Donald C.; Zimmermann, Emery. National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, KY 40511 **Neuropeptides: influence of acute and chronic effects of opiates.** Psychoneuroendocrinology (Oxford). 2(1):43-51, 1977.

The influence of neuropeptides on acute and chronic effects of opiates in vertebrates is reviewed. Beta-melanocyte stimulating hormone, corticotropic peptides (ACTH and ACTH 1-24), substance P, and desglycinamide-9-lysine vasopressin are discussed in relation to their actions on neural activity and their interactions with morphine. The following points are emphasized: 1) some of the naturally occurring polypeptides may be physiological modulators, altering synaptic excitability in a direction that is the same as or opposite to the changes in modulation produced by morphine, so as to mimic or antagonize the actions of morphine; 2) other polypeptides appear to act via different mechanisms so as to mimic or antagonize the actions of morphine, or to influence the body's response to morphine; 3) peptides that do not combine with morphine receptors in vitro can produce actions similar to morphine in vivo; and 5) it is premature to write of "the morphine receptor" as it might more appropriately be called "a morphine receptor." 51 references.

003200 Kruse, H.; Hoffmann, I.; Gerhards, H. J.; Leven, M.; Schacht, U. Hoechst Aktiengesellschaft, Abteilung fur Pharmakologie, D-6230 Frankfurt/M. 80, Germany **Pharmacological and biochemical studies with three metabolites of nomifensine.** Psychopharmacology (Berlin). 51(2):117-123, 1977.

The psychopharmacological properties of three metabolites of nomifensine (M1, M2 and M3) were investigated after oral or intraperitoneal administration in mice. In addition, inhibition of the uptake of noradrenaline (NA), dopamine (DA), and serotonin (5-HT) by these metabolites were studied in vitro in rat brain synaptosomes. In vivo, M1 (4'-hydroxynomifensine) was the most active metabolite, while M2 and M3 had little or no effect. M1 was found to: 1) reverse reserpine hypothermia; 2) antagonize tetrabenazine catalepsy; and 3) reverse oxotremorine hypothermia. In these tests, nomifensine was three to ten times more potent than M1. M1 also was found to: 1) prolong hexobarbital sleeping time; 2) prevent nicotine induced convulsions; and 3) reduce oxotremorine induced tremor. In contrast to nomifensine, M1 also had serotoninergic activity, potentiating both phenelzine induced twitching and the anticonvulsant effect of 5-hydroxytryptophan. In vitro, M1 was equipotent with nomifensine in inhibiting DA uptake and twice as active in inhibiting NA uptake. In contrast to nomifensine, M1 was also a potent inhibitor of 5-HT uptake. M2 and M3 were less active than M1 in vitro. It is suggested that M1 may have antidepressant effects and may contribute to the clinical effects of nomifensine. 15 references. (Author abstract modified)

003201 Kun, I.; Feszt, G.; Cuparencu, B.; Orban, I. Department of Pharmacology, IMF, Str. Gh. Marinescu 38, Tirgu-Mures, Rumania **Influence of predominantly antiadrenergic and antidopaminergic neuroleptics on the estrous cycle in rats.** Pharmacology (Basel). 15(2):104-111, 1977.

In experiments performed on rats, single subcutaneous doses of predominantly antidopaminergic neuroleptics (fluspirilene, pimozide, and thioproperazine in large doses) elicited persistent diestrus, i.e. pseudopreganancy. Neuroleptics with predominantly antiadrenergic action (levomepromazine, thioridazine, chlorpromazine) as well as phenoxybenzamine injected intraventricularly induced mainly prolonged estrus, i.eblocking of ovulation. Since pseudopregnancy implies a rise of prolactin secretion these results indirectly indicate that PIF secretion is stimulated by dopamine. The antiovulatory effect of the antiadrenergic agents, which involves an inhibition of the proestral LH surge, suggests that the discharge of LRF is mediated by an adrenergic mechanism. 27 references. (Author abstract)

003202 Kutscher, Charles L.; Wright, William A. Department of Psychology, Syracuse University, Syracuse, NY 13210 **Unconditioned taste aversion to quinine induced by injections of NaCl and LiCl: dissociation of aversion from cellular dehydration.** Physiology & Behavior. 18(1):87-94, 1977.

Rats were subjected to intraperitoneal injections of NaCl and LiCl prior to testing for taste aversion to quinine HCl (QHCl) to investigate unconditioned aversion to novel stimuli and role of treatment in cellular dehydration. Injection of hypertonic NaCl intraperitoneally into rats, 24 hr water deprived, increased intake of water (compared to a deprived, mock injection group) and decreased intake of a 0.01% QHCl solution, a finding which has been attributed previously to the action of cellular dehydration. This interpretation was questioned since the induced aversion to QHCl was not produced by prolonged water deprivation, which should produce marked cellular dehydration and was caused by LiCl injections which produced no cellular dehydration, as determined by measurements of hematocrit, plasma osmolality, and protein. Combined NaCl and polyethylene glycol injections into water deprived rats increased water intakes, but produced QHCl aversion even though the physiological effects of the dual injection should resemble water deprivation (i.e. cellular dehydration plus hypovolemia). These findings suggest that altering the internal state of the animal by manipulations, which may produce illness, produced unconditioned aversion to a novel stimulus. 20 references. (Author abstract modified)

003203 LaManna, J. C.; Younts, B. W., Jr.; Rosenthal, M. Department of Physiology and Pharmacology, Duke University Medical Center, Durham, NC 27710 **The cerebral oxidative metabolic response to acute ethanol administration in rats and cats.** Neuropharmacology. 16(4):283-288, 1977.

The cerebral mitochondrial oxidative metabolic response to acute ethanol administration was studied in rats and cats by noninvasive optical techniques. Acute ethanol injections caused progressive increase in the level of reduced cytochrome a,a3 (Caa); phenobarbital (PB) and chlorpromazine (CZ) had the same effects. Low ethanol (below approximately 1g/kg) increased the level of reduced nicotinamide adenline dinucleotide (NADH) and it appeared that the ethanol effect in vivo was due to a decrease in tissue activity common to central depressants. Higher ethanol doses (1 to 3g/kg) produced increased levels of NAD whereas PB and CZ each resulted in increased levels of NADH. Since many of the effects of ethanol have been attributed to the activity of its primary metabolic product, acetaldehyde, the latter's effect on energy metabolism was studied. Acetaldehyde at all effective doses produced similar changes in NAD and Caa to those of the higher ethanol doses. The oxidation of NAD at higher ethanol doses and at all doses of acetaldehyde was interpreted as a unique effect of ethanol and due to acetaldehyde. 37 references. (Author abstract modified)

003204 Larson, Alice A.; Takemori, A. E. Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455 **Effect of narcotics on the uptake of serotonin precursors by the rat brain.** Journal of Pharmacology and Experimental Therapeutics. 200(1):216-223, 1977.

The effects of several narcotic drugs on the extraction of radiolabeled serotonin precursors, tryptophan and hydroxytryptophan (5-HTP), from blood to the brain were studied in rats. Acute treatment with morphine caused a dose related decrease in the extraction of tryptophan and an increase in the extraction of 5-HTP. Naloxone alone had no effect on the extraction of either serotonin precursor but completely blocked the effects of morphine. The extractions of tryptophan and 5-HTP were not significantly altered 48 hr after chronic treatment with morphine, but the extraction of tryptophan increased significantly 72 hr after chronic morphine treatment. In equivalent doses, levorphanol decreased the extraction of tryptophan more than did its inactive isomer dextrorphan. Levorphanol increased the extraction of 5-HTP but dextrorphan had no effect. It is suggested that an increase in the rate of central serotonin synthesis after acute treatment with morphine may be due to an increased uptake of 5-HTP from the blood, while that after chronic treatment with morphine may be due to an increased uptake of tryptophan. 32 references. (Author abstract modified)

003205 Lembeck, F.; Beubler, E. Institut fur Experimentelle und Klinische Pharmakologie der Universitat Graz, Universitatsplatz 4, A-8010 Gratz, Austria **Convulsions induced by hyberbaric oxygen: inhibition by phenobarbital, diazepam and baclofen.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(1):47-51, 1977.

The anticonvulsive potencies of diazepam (DZ), phenobarbital (PB), and baclofen (BC) against convulsion induced by

hyperbaric oxygen (HBO), by isoniazid, and by strychnine were studied in mice and rats. The anticonvulsive potency of DZ was much higher than that of PB and BC against all three types of convulsions. The selective activity of DZ against isoniazid induced convulsions in rats could not be confirmed in mice, where DZ was equipotent against all three types of convulsion; the effective dose 50 ratio of PB to DZ was 400 in rats and 20 to 40 in mice. BC which did not inhibit strychnine induced convulsions was equipotent in inhibiting convulsion evoked by isoniazid and HBO in mice. The results agree with the postulated gamma-aminobutyric acid inhibitory mechanism of HBO induced convulsions, whereas they make a glycine inhibitory mechanism very unlikely. A clinical trial of DZ in HBO induced convulsions was recommended. 29 references. (Author abstract modified)

003206 Lewis, Douglas; Isaac, Lawrence. Department of Pharmacology, University of Illinois, Chicago, IL 60680 **Effects of antihistaminic drugs on feline brain monoamine metabolism.** Biochemical Pharmacology (Oxford). 26(2):133-135, 1977.

To test the hypothesis that antihistamines produce sedation, excitation and convulsions through an alteration in the balance of central monoamine metabolism, diphenhydramine and phenindamine were administered in various doses to cats and the time course of changes in monoamine metabolite levels in cerebrospinal fluid was determined. Diphenhydramine at a sedative dose did not alter 5-hydroxytryptamine or dopamine metabolism. Excitant doses of diphenhydramine elevated 5-hydroyxindolacetic acid levels, where homovanillic acid levels remained unchanged. At a convulsant dose, diphenhydramine lowered rectal temperature while elevating both 5-hydroxyindolacetic acid and homovanillic acid levels. Phenindamine, which reportedly produces only central nervous system (CNS) excitation and convulsions, caused excitation, tremor and stereotypy, while elevating 5-hydroxyindolacetic acid and homovanillic acid levels in cerebrospinal fluid. These data suggest that antihistaminic induced sedation is not due to an alteration in brain 5-hydroxytryptamine or dopamine metabolism and that only 5-hydroxytryptamine metabolism is increased during CNS excitation. Stereotypic behavior after phenindamine may occur through a dopaminergic system as reflected by elevated levels of homovanillic acid in cerebrospinal fluid. 21 references. (Author abstract modified)

003207 Liebschutz, Jack; Airoldi, Luisa; Brownstein, Michael J.; Chinn, Norma G.; Wurtman, Richard J. Lab. of Neuroendocrine Regulation, Massachusetts Institute of Technology, Cambridge, MA 02139 **Regional distribution of endogenous and parenteral glutamate, aspartate and glutamine in rat brain.** Biochemical Pharmacology (Oxford). 26(5):443-446, 1977.

The effects of monosodium glutamate, aspartatic acid and other acidic amino acids, administered alone or in combination, on the concentrations of glutamine, glutamate and aspartate in whole brain, various brain regions, and retina of rat were examined in order to assess the risk of neuronal or retinal toxicity from ingestion of these substances. Analysis of data reconfirmed previous results that glutamine acid levels vary considerably among rat brain regions and that the distribution of glutamate differs from those of glutamine and aspartate. The effects of concomitant glutamate and aspartate administration were not additive to their combined concentration in rat brain or retina, although glutamine brain levels rose significantly after glutamine administration. It is suggested that there is little basis for concern that consumption of both glutamate and aspartate would amplify risks of neuronal or retinal toxicity. 29 references.

003208 Lokhandwala, Mustafa F.; Pariani, Harish K.; Buckley, Joseph P.; Jandhyala, Bhagavan S. Department of Pharmacology, College of Pharmacy, University of Houston, Houston, TX 77004 **Involvement of central alpha-adrenoceptors in the hypotensive and bradycardic effects of (-)-delta9-trans-tetrahydrocannabinol.** European Journal of Pharmacology (Amsterdam). 42(2):107-112, 1977.

The involvement of central alpha-adrenoceptors in the hypotensive and bradycardic effects of (-)-delta9-trans-tetrahydrocannabinol (THC) was studied in cats. Administration of THC to chloralose anesthetized cats produced a decrease in blood pressure and heartrate. The hypotensive and bradycardic effects of THC were antagonized following perfusion with the alpha-adrenergic receptor blocking agent, phentolamine, while a larger dose of THC still produced significant hypotension and bradycardia. Perfusion of phentolamine caused a fall in blood pressure and heartrate which were reversible and produced blockade of central alpha-adrenergic receptors, since the dose blocked the hypotensive and bradycardic response to administration of norepinephrine. The effect of norepinephrine was still attenuated when the fall in blood pressure and heartrate observed following phentolamine had returned to control levels. The results provide evidence for the involvement of central alpha-adrenergic receptors in the hypotensive and bradycardic actions of THC and indicate that other receptor mechanisms may also be involved in mediating the responses observed following THC administration. 20 references.

003209 Luders, Hans; Bustamante, Luis A.; Pippenger, Charles E.; Goldensohn, Eli S. no address **The effects of phenytoin, phenobarbital, and carbamazepine on the experimental spike focus.** Neurology. 27(4):375, 1977.

At a meeting of the American Academy of Neurology in Atlanta, Ga in April, 1977, the effects of phenytoin (PT), phenobarbital (PB), and carbamazepine (CZ) on the experimental spike focus produced in cats by penicillin were studied. In the weak focus produced by 20,000 units/cc which permits assessment of effects on the primary spike, all 3 compounds produced a marked increase in frequency of firing and decrease in amplitude and durations of the individual spikes. With additional doses, the amplitudes and durations of the spikes decreased further, and in some instances the spikes disappeared. CZ was the most effective, abolishing spikes in all cases at drug blood levels considered within the therapeutic range in man. PT and PB did not abolish spikes at similar blood levels. PB had the least effect in increasing spike frequency, but was the most effective in reducing spike duration. All 3 drugs increased both early and late positive components of the spike. In the strong focus produced by 100,000 units/cc of penicillin, all 3 anticonvulsants abolished afterdischarges in all cases at blood levels within the therapeutic range. The high sensitivity of afterdischarging makes this model particularly useful for the testing of new potentially anticonvulsant drugs. (Author abstract modified)

003210 MacDonald, Robert L.; Barker, Jeffery L. no address **Penicillin and pentylenetetrazol selectively antagonize GABA-mediated postsynaptic inhibition of cultured mammalian neurons.** Neurology. 27(4):337, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the effects of the convulsants penicillin and pentylenetetrazol on gamma-aminobutyric acid (GABA) mediated postsynaptic inhibition of cultured mouse spinal cord neurons were studied. Both convulsants reversibly antagonized the conductance change and voltage response produced by

GABA in a dose dependent manner without affecting either resting membrane properties or the responses of the inhibitory amino acids, beta-alanine and glycine, or the excitatory amino acid glutamate. Penicillin, but not penylenetetrazol caused a delay in the time to peak and prolonged the decay time of the GABA response, suggesting that the convulsants selectively antagonized GABA through somewhat different mechanisms. The results support the hypothesis that part of the convulsant activity of the convulsants is due to their ability to selectively antagonize GABA mediated postsynaptic inhibition in the mammalian central nervous system.

003211 Magour, Samir; Coper, Helmut; Fahndrich, Christa. Institute of Neuropsychopharmacology of the Free University Berlin, Ulmenallee 30, D-1000 Berlin 19, Germany **Is tolerance to delta9-THC cellular or metabolic? The subcellular distribution of delta9-tetrahydrocannabinol and its metabolites in brains of tolerant and non-tolerant rats.** Psychopharmacology (Berlin). 51(2):141-145, 1977.

An investigation was carried out in rats to determine whether development of tolerance to the motor activity depressant effect of delta9-tetrahydrocannabinol (delta9-THC) can be correlated with changes in the distribution of delta9-THC and its metabolites in the brain. After nine intraperitoneal injections had been administered at 12 hour intervals, the maximum intensity of the motor activity depressant effect was not different from that occurring after one injection, but tolerance to the duration of effect was apparent. The subcellular distribution studies indicated that an accelerated shift in the concentrations of delta9-THC and 11 OH delta9-THC towards highly polar metabolites in the brain, rather than an increased elimination of these cannabinoids or decreased sensitivity to these compounds, may be responsible for the development of tolerance to delta9-THC. 12 references. (Author abstract modified)

003212 Marselos, M.; Nousiainen, U.; Pietikainen, S.; Hanninen, O. Department of Physiology, University of Kuopio, SF-70101 Kuopio 10, Finland **Development of rat sub-strains for studies on the control of drug metabolism.** Xenobiotica (London). 7(1/2):103, 1977.

The development of rat substrains for studies on the control of drug metabolism was discussed at a symposium entitled "Drug Metabolism -- from Microbe to Man" held in Guildford, England in April 1976. In the course of research on D-glucaric acid synthesis it was noted that induction of hepatic D-glucuronolactone dehydrogenase varied among individuals in the experimental population. It was found that a codominant autosomal gene determines the low (rr) or high (RR) inducibility of the enzymes. The implications of the different degrees of induction of drug metabolizing enzymes were assessed by measuring pentobarbital sleeping time. After pretreatment with phenobarbital rr rats were significantly more sensitive to pentobarbital than RR rats. Sleeping times were not different in the noninduced state. Results suggest that control of D-glucuronolactone and aldehyde dehydrogenases and NADPH-cytochrome-c reductase share a common nominator in the rat liver, and that this factor also influences biological responses to pentobarbital. 3 references. (Author abstract modified)

003213 Martinez, Terry T.; McNeill, John H. Division of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Univ. of British Columbia, Vancouver, B.C. V6T 1W5, Canada **The effect of theophylline on amine-induced cardiac cyclic AMP and cardiac contractile force.** Canadian Journal of Physiology and Pharmacology (Ottawa). 55(1):98-104, 1977.

The effect of theophylline on amine induced cardiac cyclic adenosine 3',5'-cyclic monophosphate (AMP) and cardiac contractile force in isolated left atria of rats was studied. In the isolated electrically driven rat atria, theophylline (0.5mmol) produced a small but significant increase in cyclic AMP content which was prevented by reserpine pretreatment. Theophylline was also found to exert a direct contractile effect, unrelated to cyclic AMP, in atria obtained from reserpine pretreated animals. The norepinephrine inotropic response was attenuated after 3 min, enhanced after 15 min, and abolished after 60 min of exposure to theophylline (0.5mmol). The maximum phenylephrine inotropic response was not significantly changed after 15 min of exposure to theophylline; however there was a slight shift to the left of the phenylephrine dose response curve. The effect of theophylline on cyclic AMP appeared to be additive with the norepinephrine and phenylephrine responses. The effect of theophylline on amine induced cardiac cyclic AMP and contractile force showed no correlation between the contractile and the cyclic AMP effects at the different times tested. It is concluded that the inotropic effects of theophylline in rat atria are not mediated through cyclic AMP; instead, the methylxanthines may exert their effects on the heart through changes in calcium metabolism. 33 references. (Author abstract modified)

003214 Matchett, J. A.; Erickson, C. K. Department of Pharmacology and Toxicology, School of Pharmacy, University of Kansas, Lawrence, KA 66045 **Alteration of ethanol-induced changes in locomotor activity by adrenergic blockers in mice.** Psychopharmacology (Berlin). 52(2):201-206, 1977.

The alteration of ethanol induced changes in spontaneous locomotor activity (SLM) by adrenergic blockers was studied in mice. SLM was stimulated by ethanol at doses of 0.5and 1.0g/kg, but depressed by a dose of 4.0g/kg. An intermediate dose (2.0g/kg) produced a biphasic effect of depression followed by stimulation. Pretreatment with central catecholamine antagonists before ethanol (2.0g/kg) gave the following results: 1) propranolol, a beta-receptor blocker, antagonized the depressant effect but had no influence on the stimulant effect; 2) phentolamine, an alpha-receptor blocker, antagonized the stimulant phase but had no effect on the depressant phase; and 3) spiroperidol, a dopaminergic blocking drug, enhanced the SLM depression caused by ethanol. The results indicate that: 1) the SLM depressant effect of ethanol may be mediated by central beta type receptors; 2) the SLM stimulant effect of ethanol may be mediated by central alpha type receptors; and 3) at least part of the ethanol action may be due to dopaminergic mechanisms. 20 references. (Author abstract modified)

003215 Matsui, Yoshiki; Deguchi, Takehiko. Central Research Laboratories, Sankyo Co. Ltd., Hiromachi 1-chome Shinagawa-ku, Tokyo 140, Japan **Effects of gabaculine, a new potent inhibitor of gamma-aminobutyrate transaminase, on the brain gamma-aminobutyrate content and convulsions in mice.** Life Sciences. 20(7):1291-1296, 1977.

Effects of gabaculine (5-amino cyclohexa-1,3-dienyl carboxylic acid), a new potent inhibitor of gamma-aminobutyrate (GABA) transaminase, on the brain GABA content and convulsions were studied in mice. Gabaculine injected intraventricularly elevated brain GABA content for a long period. Three hrs after treatment with gabaculine, picrotoxin and thiosemicarbazide induced convulsions were prevented, but not electroshock induced convulsions. Intraperitoneal injection of gabaculine also increased brain GABA content. Thus gabaculine seems to be a useful tool for investigating the GABA function in the brain. 8 references. (Author abstract)

003216 Matsuyama, Steven S.; Fu, Tsu-ker; Jarvik, Lissy F. Veterans Administration Hospital, Brentwood, CA **Chromosome studies before and after the acute administration of morphine.** Behavior Genetics. 7(1):76-77, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, chromosomes were examined before and after the acute administration of morphine in healthy adult male volunteers, members of 10 monozygotic twin pairs. Subjects were studied on two experimental days; on one day placebo was given and on the other morphine. Blood samples for leukocyte cultures were obtained on the morning of each experimental day prior to the administration of drug and again 4 hours later. No increase in the frequency of breaks was found for either morphine or placebo when predrug and postdrug administration values were compared. Further, intratwin and intertwin pair comparisons did not reveal any evidence of a genetic predisposition to chromosome damage in the small sample used. (Author abstract modified)

003217 McCulloch, James; Harper, A. Murray. Wellcome Surgical Research Institute, University of Glasgow, Glasgow G61 1QH, Scotland **Cerebral circulatory and metabolism changes following amphetamine administration.** Brain Research (Amsterdam). 121(1):196-199, 1977.

To investigate the relationship between monoamines and cerebral circulation, amphetamines were administered to the baboon and the effects of the pharmacological release of catecholamines on cerebral blood flow were measured. At least three determinations of cerebral blood flow and metabolism were made prior to any drug administration and the mean of these served as baseline values. D-amphetamine sulphate dissolved in saline was injected intravenously over a period of 2 min on a total of five occasions. Cerebral blood flow and metabolism were measured at intervals thereafter. The administration of amphetamine resulted in significant elevations in both cerebral oxygen and cerebral glucose metabolism and by an increase in cerebral tissue perfusion. At no time immediately following the amphetamine administration was dilatation in the cerebral bed not accompanied by a metabolic increase. The mechanism by which perfusion is coupled to the metabolic needs of the brain remains controversial. Thus little evidence was found to dispute the hypothesis that stimulation of metabolism leads to a buildup of vasodilatatory metabolites and that these provoke the dilatation of cerebral resistance vessels. 15 references.

003218 Mehendale, H. M. Dept. of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS 39216 **Effect of preexposure to kepone on the biliary excretion of imipramine and sulfobromophthalein.** Toxicology and Applied Pharmacology. 40(2):247-259, 1977.

The effect of kepone on the biliary excretion of imipramine (IMP) was studied using isolated perfused rat liver preparations obtained from control and kepone pretreated animals. Biliary excretion of endogenously formed polar metabolites of IMP was markedly suppressed (70%) by preexposure to kepone at 200ppm in daily ration for 8 days. In vitro addition of kepone to the perfusate of untreated liver preparations elicited 20% decrease in the biliary excretion of endogenously formed metabolites. At concentrations up to 5x1 0-5 M, kepone was without any discernible effect. The marked suppression of biliary elimination of endogenously formed metabolites is unrelated to the rate of metabolism of IMP. Furthermore, the biliary excretion of exogenously provided polar metaolites of IMP was also suppressed (61%) by preexposure to kepone. This suppression of biliary excretion of IMP metabolites was accompanied by an increase in the bile flow, suggesting a dichotomy between bile secretion and biliary excretion. In vitro addition of kepone also resulted in suppression (48%) of biliary elimination of exogenously proved metabolites of IMP. In the experiments in which kepone was added, bile flow was unaffected. Biliary excretion of sulfobromophthalein (BSP) was unaffected by preexposure to kepone, suggesting that kepone induced impairment of hepatobiliary function may not be detected by BSP clearance tests. In addition, different mechanisms might be involved in the transport of IMP metabolites and BSP across the biliary canaliculi. From these results, it is suggested that the kepone induced impairment of hepatobiliary function may be located at the site of transfer of metabolites across the bile canaliculi. 33 references. (Author abstract modified)

003219 Meller, E.; Friedman, E.; Schweitzer, J. W.; Friedhoff, A. J. Millhauser Laboratories of the Department of Psychiatry, New York University Medical Center, New York, NY 10016 **Tetrarydro-beta-carbolines: specific inhibitors of type A monoamine oxidase in rat brain.** Journal of Neurochemistry (Oxford). 28(5):995-1000, 1977.

The specific inhibition of type A monoamine oxidase (MAO) by tetrahydro-beta-carbolines was studied in rat hypothalamus. Tetrahydro-beta-carboline (THBC) and 6-methoxy-THBC, 2-methyl-THBC, and 9-methyl-THBC competitively inhibited the oxidative deamination of serotonin (5-HT) at micromolar concentrations in vitro, but effective inhibition of phenethylamine (PEA) deamination was attained only at or near millimolar concentrations. The inhibitor potencies of 6-hydroxy-THBC and 6-hydroxy-2-methyl-THBC were about one tenth that of THBC. 5-HT deamination was also specifically inhibited by 3-amino-, 6-methoxy-3-amino-, and 6-hydroxy-3-aminotetrahydrocarbazole, but these compounds were about tenfold weaker than THBC. Tetrahydroisoquinolines and aminotetralins did not exhibit a marked differential inhibitory effect, although a general tendency to greater effectiveness as 5-HT inhibitors was seen. Significant reductions of type A but not type B MAO activity were also observed after the administration of THBC and its 6-methoxy derivative to rats. 30 references.

003220 Meltzer, Herbert Y.; Paul, Steven M.; Fang, Victor S. Department of Psychiatry, University of Chicago Pritzker School of Medicine, 950 East 59th Street, Chicago, IL 60637 **Effect of flupenthixol and butaclamol isomers on prolactin secretion in rats.** Psychopharmacology (Berlin). 51(2):181-183, 1977.

The effects of the antipsychotic agents cis alpha-flupenthixol and dextrobutaclamol and their nonantipsychotic isomers, trans beta-flupenthixol and levobutaclamol, on plasma prolactin levels were studied in rats. The active antipsychotic drugs were many times more active in elevating rat plasma prolactin than were the therapeutically ineffective isomers. The results support the hypothesis that the dopamine (DA) receptors that mediate the effects of DA on prolactin secretion are similar to those that mediate the antipsychotic effect of neuroleptic drugs. 21 references. (Author abstract modified)

003221 Meltzer, Herbert Y.; Fang, Victor S. Dept. of Psychiatry, University of Chicago, Pritzker School of Medicine, Chicago, IL 60637 **Effect of gamma-butyrolactone and baclofen on plasma prolactin in male rats.** Biochemical Pharmacology (Oxford). 26(7):645-646, 1977.

In order to determine if endogenous gamma-hydroxybuytrate (GHB) inhibits impulse flow in the dopaminergic (DA) neurons of the hypothalamus via stimultation of an inhibitory gamma-aminobutyric acid (GABA) mechanism, thereby increasing plasma prolactin levels, plasma prolactin levels were determined after intraperitoneal injection in male rats of: 1) the GHB precursor gamma-butyrolactone (GBL); 2) the putative GABA agonist baclofen; 3) the DA receptor blocker trifluoperazine; and 4) the DA synthesis inhibitor alpha-methylparatyrosine (AMPT) methyl ester. High doses of GBL and baclofen produced plasma prolactin increases comparable to those produced by trifluoperazine and greater than those produced by AMPT methyl ester. However, lower doses of GBL which have been reported to reduce the activity of DA neurons failed to raise plasma prolactin levels. It is posited that the effect of GHB on plasma prolactin may be a nonspecific anesthetic effect similar to that produced by ether and barbiturates. 17 references.

003222 Meltzer, Herbert Y.; Fang, Victor S.; Simonovich, Miljana; Paul, Steven M. Department of Psychiatry, University of Chicago Pritzker School of Medicine, Chicago, IL **Effect of metabolites of chlorpromazine on plasma prolactin levels in male rats.** European Journal of Pharmacology (Amsterdam). 41(4):431-436, 1977.

The effects of intramuscular chlorpromazine and six of its metabolites on plasma prolactin levels were compared in male rats. 7-Hydroxychlorpromazine produced increases in plasma prolactin equivalent to those produced by chlorpromazine. 8-Hydroxychlorpromazine, 7,8-dihydroxychlorpromazine, 8-hydroxy-7-methoxychlorpromazine, 7-methoxychlorpromazine and chlorpromazine sulfoxide had no effect on plasma prolactin levels in doses of 5mg/kg. 8-Hydroxychlorpromazine, 7-methoxychlorpromazine, 7,8-dihydroxychlorpromazine and chlorpromazine sulfoxide had no effect even after 25mg/kg. The capacity of these compounds to increase rat plasma prolactin correlates highly with other methods of determining potential antipsychotic activity of chlorpromazine and its derivatives. 30 references. (Author abstract modified)

003223 Molter, D. J. Department of Toxicology, University of the Saarland, D-6650 Homburg/Saar, Germany **On the mechanism of pulmonal hypertension induced by anorexic agents.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R32, 1977.

A study of the mechanism by which anorexic agents produce pulmonary hyptertension is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany, in March 1977. The effects of dextroamphetamine, amonorex, amphetaminil, phenmetrazine, propylhexedrine, phentermine, chlorphentermine, levoephedrine, dextro-norpseudoephedrine, oxyphedrine, naphazoline, levo-norephindrine, dextro-pseudoephedrine, levo-pseudoephedrine, fenfluramine, fenethyline, fenproporex, and diethylaminopropiophenon on the uptake of radiolabeled norepinephrine (noradrenalin, NA) and serotonin (5-hydroxytryptamine, 5-HT) in the isolated guinea-pig heart were examined. All of the sympatholmimetic agents tested produced a 50% decrease in NA uptake; however, only the anorexic agents also inhibited 5-HT uptake. It is suggested that the inhibition of NA and 5-HT uptake by the anorexic drugs is related to their ability to produce pulmonary hypertension. (Author abstract modified)

003224 Montoya, Gonzalo A.; Riker, William K.; Russell, Nancy J. Department of Pharmacology, Institute of Basic Medical Sciences, University of Concepcion, Box 2927, Concepcion, Chile **Stimulus-bound repetitive synaptic firing caused by ethanol in sympathetic ganglion.** Journal of Pharmacology and Experimental Therapeutics. 200(2):320-327, 1977.

The effects of ethanol on synaptic transmission, preganglionic axonal fibers and the ganglion cell were examined by extracellular and intracellular recording in isolated bullfrog sympathetic ganglia. Within the concentration range 0.2to 0.8M, ethanol caused stimulus-bound repetitive postganglionic responses (SBR) to single preganglionic stimuli. The presynaptic origin of ethanol induced SBR was confirmed by recordings of repetitive synaptic potential responses to single stimuli, and by absence of repetitive responses in myelinated preganglionic axons and in ganglion cells stimulated antidromically. Ethanol acted synergistically with Cs+ to produce SBR more intense than that caused by either agent alone. The postganglionic SBR caused by ethanol was suppressed by concentrations of d-tubocurarine, lidocaine, or tetraethylammonium that had little or no effect on synaptic transmission. Ethanol also blocked synaptic transmission, but this occurred secondary to the initial excitatory effects, and in the concentration range 0.4to 1.0M. The present data, together with previous studies of ethanol at neuromuscular junction, indicate that synaptic excitatory effects of ethanol are unrelated to hyperosmolarity or cholinesterase inhibition and represent a primary action of ethanol on prejunctional nerve endings. 24 references. (Author abstract)

003225 Morzorati, Sandra L; Barnes, C. D. Department of Life Sciences, Indiana State University, Terre Haute, IN 47809 **Sensitivity of components of the central vestibular complex to pentobarbital.** Neuropharmacology. 16(4):295-298, 1977.

The sensitivity of monosynaptic (MS) and polysynaptic (PS) linkages of the central vestibular complex to pentobarbital was studied in decerebrated cats. Individual branches of the VIIIth nerve were electrically stimulated and MS and PS potentials were recorded from the ascending medial longitudinal fasciculus (MLF). Both the MS and PS discharges of the MLF were depressed by as little as 4mg/kg of pentobarbital; at anesthetic doses, the depression of both responses was to about 25% of the control amplitude. Single units in the vestibular nuclei which then project in the ascending MLF also discharged monosynaptically and polysynaptically to stimulation of individual vestibular nerve branches. The responses of any of the semicircular canals could be inhibited by conditioning the utricular nerve 4 msec prior to canal nerve stimulation. Pentobarbital in doses of only 3 to 4mg/kg depressed both MS and PS discharges. The MS discharge of the test canal was still functional when the PS responses had already failed. However, the presumed multisynaptic path that mediated the conditioned inhibition was persistent. The data indicate that pentobarbital influences both pathways to a similar extent and that at anesthetic levels, the responses seen following vestibular nerve stimulation represent only a fraction of the MS pathways and include a substantial number of PS pathways. 7 references. (Author abstract modified)

003226 Myers, R. D.; Metcalf, G.; Rice, J. C. Department of Psychological Sciences, Purdue University, West Lafayette, IN 47907 **Identification by microinjection of TRH-sensitive sites in the cat's brain stem that mediate respiratory, temperature and other autonomic changes.** Brain Research (Amsterdam). 126(1):105-115, 1977.

Thyrotropin releasing hormone (TRH) sensitive sites in the cat's brainstem that mediate respiratory temperature, and other autonomic changes were studied by microinjecting TRH

at 347 individual sites scattered throughout the hypothalamus and mesencephalon. Polypnea, hypothermia, vocalization, salivation, defecation, and vasodilation were evoked by TRH injected only at loci in the mesencephalon, principally in the reticular substance. TRH failed to lower body temperature when it was infused at the same sites in the anterior hypothalamus at which norepinephrine produced its characteristic hypothermia. The results suggest that TRH induced hypothermia is a secondary effect of tachypnea which results from the action of the tripeptide on the mesencephalic respiratory autonomic mechanism. 31 references. (Author abstract modified)

003227 Nagy, Adam. Department 2, Lillhagen's Mental Hospital, S-42203 Hisings Backa, Sweden **Blood and brain concentrations of imipramine, clomipramine and their monomethylated metabolites after oral and intramuscular administration in rats.** Journal of Pharmacy and Pharmacology (London). 29(2):104-107, 1977.

Blood and brain concentrations of imipramine, clomipramine and their monomethylated metabolites (desipramine and desmethylclomipramine) were measured in the brain, blood plasma and blood cells after oral and intramuscular administration to rats. The concentrations of the metabolites were higher and the concentrations of the parent substances lower after oral than after parenteral administration, both in blood and in brain. In brain imipramine, desipramine and clomipramine during continuous treatment exceeded their plasma concentrations by six to ten times. The corresponding figure for desmethylclomipramine was 1.7. The extent of accumulation of the investigated substances in the brain was independent of the route of administration. 10 references. (Journal abstract modified)

003228 Naik, S. R.; Amladi, S. R.; Sheth, U. K. Department of Pharmacology, Seth G. S. Medical College, Parel, Bombay, 400 012, India **Possible involvement of 5-hydroxytryptamine and cyclic-AMP in tolerance to tremorine analgesia in mice.** Psychopharmacology (Berlin). 52(2):213-216, 1977.

The possible involvement of 5-hydroxytryptamine (5-HT) and adenosine-3′,5′-monophosphate (cAMP) in tolerance to tremorine analgesia in mice was studied by the hot plate and tail clip methods. Reduction in 5-HT levels in brain by parachlorophenylalanine pretreatment decreased the effective dose 50 of tremorine analgesia in tremorine tolerant mice. 5-HT, L-dihydroxyphenylalanine, or alpha-methyl-para-tyrosine did not influence the analgesic response to tremorine in tremorine tolerant animals. However, theophylline enhanced the tolerance to tremorine analgesia. It was concluded that brain 5-HT and cAMP are probably involved in tremorine tolerance, whereas neither noradrenaline nor dopamine is involved in the phenomenon. 15 references. (Author abstract modified)

003229 Nedergaard, Ove A.; Schrold, Jorgen. Institute of Pharmacology, University of Odense, J.B. Winslowsvej 19, DK-5000 Odense, Denmark **The mechanism of action of nicotine on vascular adrenergic neuroeffector transmission.** European Journal of Pharmacology (Amsterdam). 42(4):315-329, 1977.

To determine the site and mechanism of action of nicotine on sympathetic neuroeffector transmission in the isolated pulmonary artery of the rabbit a series of experiments were undertaken. Nicotine and cocaine potentiated the constrictor response elicited by electrical field stimulation of postganglionic adrenergic neurones. The potentiation was reversible and in the case of nicotine, no tachyphylaxis developed. The nicotine induced potentiation was characterized by a rapid onset and an initial, transitory peak, while the enhancement caused by cocaine progressed more slowly and was monophasic. Hexamethonium and (+)-tubocurarine prevented the potentiation caused by nicotine. Nicotine did not prevent the adrenergic neurone blocking effect of bretylium on the response to field stimulation. Nicotine increased the stimulation induced outflow of tritium from pulmonary artery preloaded with 3H-noradrenaline. Contractions of the artery elicited by tyramine were enhanced by pargyline, unaltered by nicotine and blocked by cocaine. Nicotine did not alter the concentration/response curve of exogenous noradrenaline while cocaine moved it to the left. The accumulation of 3H-noradrenaline by rabbit isolated aorta was not altered by nicotine, hexamethonium and (+)-tubocurarine. The accumulation of 3H-nicotine by the aorta was much lower than that seen with 3H-noradrenaline. The disposition of the 3H-nicotine accumulation into adventitia and media was concentration independent. These results suggest: 1) that nicotine potentiates the neurogenic vasoconstriction response in part by increasing the stimulation/induced release of transmitter from adrenergic neurone terminals; 2) that the site of the nicotinic receptors mediating this action is located on the outer surface of the neurones; and 3) that the potentiation is not due to blockade of noradrenaline reuptake. 48 references. (Author abstract)

003230 Nordberg, Agneta. Department of Pharmacology, Faculty of Pharmacy, University of Uppsala, Box 573, S-75123 Uppsala, Sweden **Effect of oxotremorine and sodium pentobarbitone on the pharmacokinetics of intravenous tracer doses of radioactive choline.** Journal of Pharmacy and Pharmacology (London). 29(2):96-98, 1977.

The effects of oxotremorine and sodium pentobarbitone on the pharmacokinetics of intravenous tracer doses of radioactive choline were investigated in mice. Oxotremorine increased and sodium pentobarbiton decreased the initial brain uptake of intravenously injected radioactive choline (3H-Ch). The effects are explained by hemodynamic changes since a corresponding increase and decrease in the plasma concentration of 3H-Ch were found. This is important to know when 3H-Ch is used for estimation of acetylcholine turnover in the brain. The drugs did not affect the distribution of radioactivity (3H) between plasma and erythrocytes. 13 references. (Journal abstract modified)

003231 Obermeier, F.; Strubelt, O. Abteilung fur Toxikologie, Medizinische Hochschule Lubeck, Ratzeburger Allee 160, D-2400 Lubeck, Germany **On the mechanism of enhanced sensitivity to hepatotoxic agents induced by ethanol.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R15, 1977.

A study of the mechanism by which enhanced sensitivity to hepatotoxic agents is induced by ethanol is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. The hepatotoxic effects of carbon tetrachloride, paracetamol, Bromobenzene, thioacetamide, and allyl alcohol were enhanced in mice pretreated with ethanol. Pretreatment with ethanol did not increase the hepatotoxic actions of alpha-amanitine or phalloidin in mice or of D-galactosamine in guinea-pigs. Carbon tetrachloride produced greater increments in serum enzyme levels in rats drinking an ethanol solution for 1 week to 3 weeks than in water drinking controls. Ethanol did not influence liver glutathione levels in mice but increased aniline hydroxylation. The ethanol induced increase of

microsomal aniline hydroxylation in mice could be antagonized by treatment with dithiocarb. Dithiocarb also inhibited the hepatotoxic effects of carbon tetrachloride in these animals. It is suggested that the enhanced sensitivity to hepatotoxic agents after treatment with ethanol may be due to an enhanced microsomal activation of these substances. (Author abstract modified)

003232 Oka, Tetsuo; Negishi, Keiko. Department of Pharmacology, School of Medicine, Tokai University, Isehara, Kanagawa 259-11, Japan **Effect of neurohumoral modulators on the morphine-induced hyperthermia in non-tolerant rats.** European Journal of Pharmacology (Amsterdam). 42(3):225-229, 1977.

The effect of neurohumoral modulators on morphine induced hyperthermia in nontolerant rats was studied. In contrast to commonly used rats, in which morphine induced dose dependent changes in body temperature, the initial administration of morphine to male Wistar rats purchased from Shizudokyo (Hamamatsu, Japan) produced a consistent and prominent hyperthermia. The hyperthermia was mediated via an action of the typical morphine receptors since it was completely prevented by a specific narcotic antagonist, naloxone. Pretreatment of the rats with p-chlorophenylalanine, alpha-methyltyrosine, phenoxybenzamine, or propranolol did not alter the hyperthermia. In contrast, administration of either tertiary or quaternary anticholinergic drugs such as scopolamine, atropine, methscopolamine, and methylatropine significantly inhibited the hyperthermia. The results suggest that morphine causes hyperthermia in some strains of rats by a cholinergic mechanism and the involvement of an adrenergic or serotonergic mechanism in this case appears unlikely. 11 references. (Author abstract modified)

003233 Osumi, Yoshitsugu; Muramatsu, Ikunobu; Fujiwara, Motohatsu. Department of Pharmacology, Faculty of Medicine, Kyoto University, Kyoto 606, Japan **The effects of destruction of noradrenergic ascending ventral bundles and tetrabenazine on formation of stress-induced gastric ulcer.** European Journal of Pharmacology (Amsterdam). 41(1):47-51, 1977.

The possibility that hypothalamic noradrenaline (NA) plays a role in the formation of gastric ulcers under physical stress via ventral bundles (VB) was examined in rats after bilateral destruction of VB. After 3 h restraint stress, ulcerative changes were observed in the stomach of sham operated rats and NA contents in the hypothalamus and cerebral cortex was decreased. VB lesioning inhibited the stress induced decrease of NA in the hypothalamus. Ulcer indices in animals 1 or 7 days after VB lesioning did not differ from those of controls. Pretreatment of sham operated controls with tetrabenazine enhanced the stress induced decrease of NA in the brain and exacerbated the gastric ulceration. VB lesioning completely blocked these effects of tetrabenazine. It is suggested that the tetrabenazine induced mobilization of hypothalamic NA via VB causes an aggravation of gastric ulceration. 14 references. (Author abstract modified)

003234 Owen, F.; Bourne, Rachel C.; Lai, J. C. K.; Williams, R. Division of Psychiatry, Clinical Research Centre, Harrow HA1 3UJ, England **The heterogeneity of monoamine oxidase in distinct populations of rat brain mitochondria.** Biochemical Pharmacology. 26(4):289-292, 1977.

The characteristics of monoamine oxidase (MAO) in distinct populations of rat brain mitochondria were investigated. The three fractions of mitochondria, which were isolated by centrifugation in a Ficoll-sucrose discontinuous gradient, showed differential activity towards 5-hydroxytryptamine (a type A MAO substrate) and phenylethylamine (a type B MAO substrate). There were also clear differences in the inhibition characteristics of MAO with the specific inhibitors clorgyline and deprenyl. It is suggested that rat brain mitochondria are not homogeneous with respect to their complements of MAO, and that the differences are not due to artifacts produced by the isolation procedure. 23 references. (Author abstract modified)

003235 Pardo, Jose V.; Creese, Ian; Burt, David R.; Snyder, Solomon H. Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **Ontogenesis of dopamine receptor binding in the corpus striatum of the rat.** Brain Research (Amsterdam). 125(3):376-382, 1977.

The ontogenesis of dopamine receptor binding in the corpus striatum was studied in rat pups and adults. A series of drugs, including dopamine, apomorphine, norepinephrine, isoproterenol, fluphenazine, chlorpromazine, and promethazine, were evaluated for their ability to compete at 3H-haloperidol (HA) binding sites in the rat striatal membranes. The results indicated that specific HA binding involves the same sites in rat corpus striatum as in bovine caudate membranes, presumably postsynaptic dopamine receptors. HA binding was between 10-15% of adult levels at birth and showed little change until 7 days, when it increased rapidly, more than doubling between 7 and 14 days and then tripling by 28 days. There was little change in binding between 28 days and young adult values. Striatal membranes of aged rats (greater than 180 days) bound HA at only 65% of young adults levels. The above values were computed per unit wet weight of tissue; expressed per whole corpus striatum binding increased 100 fold between birth and 28 days, and then was constant in young adults. Protein concentration in the striatal membrane preparations increased 2.5fold between birth and 28 days with a further 20% augmentation in adults, and decline to 28 day levels in aged rats. 24 references.

003236 Parmar, Surendra S.; Chaudhary, Mahima; Chaudhary, Sunil K.; Spiro, Herzl R. Milwaukee County Mental Health Center, 9191 Watertown Plank Road, Milwaukee, WI 53226 **Anticonvulsant activity and selective inhibition of NAD-dependent oxidations by 1,4-disubstituted piperazines.** Pharmacology (Basel). 15(2):112-117, 1977.

Several 1-(1-aryl-3-ethylthiocarbamido)-4-(arylaminothiocarbonyl)piperazines were synthesized, characterized by their sharp melting points and elemental analyses and evaluated for anticonvulsant activity. All disubstituted piperazines at a dose of 100mg/kg i.p. provided 10 to 90% protection against pentylenetetrazol induced convulsions in mice. These disubstituted piperazines selectively inhibited the in vitro oxidation of nicotinamide adenine dinucleotide (NAD) dependent oxidation of pyruvate, alpha-ketoglutarate, beta-hydroxybutyrate and NADH by rat brain homogenates. The NAD independent oxidation of succinate remained unaltered. The anticonvulsant activity possessed by disubstituted piperazines was unrelated with their ability to selectively inhibit respirator activity of rat brain homogenates. 8 references. (Author abstract)

003237 Percy, Vivienne A.; Shanley, Brian C. no address **Lack of effect of phenobarbitone treatment on metabolism and brain uptake of delta-aminolaevulinic acid in rats.** Biochemical Pharmacology (Oxford). 26(8):802-803, 1977.

A study of the lack of effect of phenobarbitone treatment on metabolism and brain uptake of delta-aminolaevulinic acid (ALA) was conducted in rats, investigating hypotheses of neurotoxicity. Two groups of female Wistar rats were maintained individually and monitored for urine collection after treatment by: 1) starvation, ad lib drinking water, injection with phenobarbitone, and administration of ALA; and 2) starvation, ad lib drinking water, injection with saline solution, and administration of ALA. After decapitation, blood, liver, and brain were removed, and urine samples stored for analysis. The ALA content of serum, brain, and liver, and the ALA and porphobilinogen content of the urine were determined spectrophotometrically. Results demonstrated that neither acute nor chronic administration of ALA to rats produced significant neuropathic effects, and do not support the hypothesis that porphyrinogenic drugs may precipitate acute neuropathic effects in the hereditary hepatic porphyrias through altering porphyrin precursor metabolism or uptake of these compounds by neural tissue. 20 references.

003238 Persson, Sven-Ake. Department of Pharmacology, University of Umea, S-901 87 Umea, Sweden **Effects of LSD and 2-bromo LSD on striatal DOPAC levels.** Life Sciences. 20(7):1199-1206, 1977.

The effects of d-lysergic acid diethylamide (LSD) and 2-bromo lysergic acid diethylamide (BLSD) on striatal 3,4-dihydroxyphenylacetic acid (DHPA) levels in rats were studied. LSD and BLSD administration caused a shortlasting increase in DHPA levels in the rat striatum; BLSD was the most potent. There was a concomitant increase in the striatal in vivo tyrosine hydroxylation as measured by 3,4-dihydroxyphenylalanine (DOPA) accumulation after decarboxylase inhibition. These results suggest that LSD and BLSD increase the impulse flow in the nigro neostriatal pathway probably by central dopamine receptor antagonism. However, 4 hrs after LSD the DHPA level was decreased, while the DOPA accumulation was not. Thus the effect of LSD on the dopaminergic system appears not to be limited to a pure receptor antagonism. The possibility exists that the effect of LSD on the nigro neostriatal pathway is secondary to its effect on the central 5-hydroxytryptaminergic system. 20 references. (Author abstract modified)

003239 Persson, Sven-Ake. Department of Pharmacology, University of Umea, S-901 87, Umea, Sweden **The effect of LSD and 2-bromo LSD on the striatal dopa accumulation after decarboxylase inhibition in rats.** European Journal of Pharmacology (Amsterdam). 43(1):73-83, 1977.

LSD and BOL were equipotent in increasing the in vivo tyrosine hydroxylation in the striatum as measured by the accumulation of DOPA after inhibition of neuronal decarboxylase. However, with 2 to 4mg/kg doses, the maximum effect of BOL was larger than that of LSD. LSD and BOL antagonized the apomorphine induced decrease of DOPA accumulation, without affecting the haloperidol induced increase. LSD-like apomorphine inhibited the increase of DOPA accumulation seen after reserpine, cerebral hemisection and after gamma-butyrolactone (GBL). The effect of apomorphine in rats given GBL was blocked by haloperidol, but not by BOL and promethazine, whereas that of LSD was inhibited by haloperidol, BOL, and promethazine. These findings suggest that LSD and BOL directly affect nigro neostriatal dopamine neurons. LSD therefore appears to be apartial agonist and BOL a pure antagonist at dopamine autoreceptors. It is proposed in addition that LSD activates and BOL blocks 5 HT receptors that control DOPA formation. 39 references. (Author abstract)

003240 Pert, Agu; Sivit, Carlos. Adult Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20014 **Neuroanatomical focus for morphine and enkaphalin-induced hypermotility.** Nature (London). 265(5595):645-647, 1977.

In order to determine if the nucleus accumbens (NA) in the limbic forebrain is an important focus for the excitatory effects of opiates on behavior, morphine, D-Ala4-enkephalinamide, and apomorphine were injected directly into the NA of male Spargue-Dawley rats. Apomorphine produced an immediate increase in horizontal and vertical locomotor activity which dissipated rapidly over a 90 minute period. Morphine produced a more gradual increase in activity which persisted up to 6 hours after injection. Excitatory effects of enkaphaline had a gradual onset but were less persistent than morphine. Apomorphine was antagonized by haloperidol pretreatment but not by haloxone, while morphine effects were antagonised by naloxone pretreatment but not by haloperidol. This suggests the existence in the brain of a tonically active enkaphalinergic system with a role in modulating some aspects of motor activity and that opiates produce excitatory effects that are dissociated from direct dopaminergic actions in the rat forebrain. It is suggested that parallel neurohumoral systems may exist in the forebrain to regulate motility, one encoded by dopamine and the other by enkephalin. 22 references.

003241 Picotti, Giovanni B.; Carruba, Michele O.; Zambotti, Fernanda; Mantegazza, Paolo. Department of Pharmacology, School of Medicine, University of Milan, Via Vanvitelli 32, I-20129 Milano, Italy **Effects of mazindol and d-fenfluramine on 5-hydroxytryptamine uptake, storage and metabolism in blood platelets.** European Journal of Pharmacology (Amsterdam). 42(3):217-224, 1977.

The effects of mazindol (MZ) and d-fenfluramine (FEN) on 5-hydroxytryptamine (5-HT) uptake, storage, and metabolism were studied in guinea pig blood platelets. MZ induced a dose related inhibition of the uptake of labeled 5-HT and was more potent than FEN. MZ and FEN decreased 5-hydroxyindoleacetic acid formation in intact platelets but not in sonicated ones. The inhibitory effects of both drugs appeared to be competitive in nature and were markedly reduced in platelets suspended in plasma instead of in Tyrode solution. MZ neither decreased the stored endogenous 5-HT nor caused efflux of the labeled amine from preloaded platelets, whereas FEN induced a significant release of the amine. It was concluded that MZ, like FEN, competes with 5-HT for the same transport mechanisms at the cytoplasmic membrane level but this effect is not accompanied, as is the case with FEN, by a concomitant release of the amine. 23 references. (Author abstract modified)

003242 Pragay, Eva Bakay; Mirsky, Allan F. Laboratory of Neuropsychology, Division of Psychiatry, Boston University School of Medicine, Boston, MA 02215 **Effect of secobarbital and chlorpromazine on cortical and subcortical visual-evoked potentials in the monkey.** Psychopharmacology Bulletin. 13(2):61-64, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, the effect of secobarbital (SECO) and chlorpromazine (CPZ) on cortical and subcortical visual evoked potentials (VEP) was studied in the monkey. Four monkeys were prepared with implanted electrodes on the dura overlying the visual cortex and in the superior colliculus. VEP were recorded from the two structures before and after administration of SECO and CPZ in doses that produced periods of intermittent or complete response failure. The VEP from the

visual cortex showed enhancement in certain components under both SECO and CPZ, but the VEP from the superior colliculus appeared enhanced under SECO and diminished under CPZ. The reduced colliculus VEP under CPZ may help to explain the diminished responsiveness to visual stimuli that is seen with this drug. This behavioral effect may be mediated by one or more of the group of structures that comprise the "secondary" visual system. This subcortical stimulus filtering effect of CPZ may be relevant to the understanding of its efficacy as an antipsychotic agent. 6 references.

003243 Pugsley, T. A.; Lippmann, W. Biochemical Pharmacology Department, Ayerst Research Laboratories, Box 6115, Montreal, Quebec, H3C 3JI, Canada **Effects of 1-alkyl-1,2,3,4-tetrahydrocarbazole-1-ethanamines and related compounds, potential antidepressants, on biogenic amine uptake mechanisms.** Experientia (Basel). 33(1):57-59, 1977.

A new series of compounds structurally related to the potential antidepressant tandamine, i.e. the 1-alkyl-1,2,3,4-tetrahydrocarbazole-1-ethanamines and related compounds (cycloalkamoindoles), were examined for their inhibitory activities on noradrenaline (NA) and serotonin (5-HT) reuptake mechanisms. There is considerable evidence that the antidepressive action of certain known tricyclic antidepressants may be due to their abilities to cause inhibition of the neuronal reuptake of NA, 5-HT, or both. The potency of the most effective compound is equivalent to desimipramine in its ability to inhibit the NA uptake mechanism and lacking an appreciable ability to affect 5-HT mechanisms. Clinically, it is of potential use in treating endogenously depressed patients. 15 references.

003244 Puri, S. K.; Volicer, L.; Lal, H. Department of Pharmacology, Boston University School of Medicine, Boston, MA 02118 **Effect of apomorphine on dopamine turnover and adenosine 3′,5′-monophosphate content in striatum of morphine-dependent rats.** Neuropharmacology (Oxford). 16(3):205-209, 1977.

The effects of dopamine (DA) receptor stimulation by apomorphine on striatal DA turnover and on striatal cyclic adenosine 3′,5′-monophosphate (cyclic-AMP) levels were studied in control and in morphine-dependent rats withdrawn for 72 hr. In morphine withdrawn rats, apomorphine reduced striatal DA turnover to a markedly greater extent than in non-dependent controls. However, apomorphine increased striatal cyclic-AMP levels less significantly in morphine withdrawn animals than in controls. It is suggested that apomorphine differentially affects DA turnover and cyclic-AMP levels in the striatum of morphine dependent rats. 37 references. (Author abstract modified)

003245 Quirce, Carlos M.; Levine, Richard M.; Maickel, Roger P. Section of Pharmacology, Medical Sciences Program, Indiana University School of Medicine, Bloomington, IN 47401 **Drug interactions on body temperature maintenance in the mouse.** Research Communications in Chemical Pathology and Pharmacology. 16(4):621-628, 1977.

A study of interactions of d-amphetamine and caffeine in cold exposed mice was undertaken to study the drug interactions and the possible interference with thermoregulation. Exposure of mice to an environmental temperature leads to a loss of body temperature and death in 5 to 6 hours. Intraperitoneal injection of water or d-amphetamine exacerbates this effect, while caffeine has a modest antagonistic effect. The combination of caffeine and d-amphetamine is synergistic and leads to a rapid loss in body temperature with death occurring in less than 3 hours. 13 references. (Author abstract modified)

003246 Raabe, W.; Gumnit, R. J. Department of Neurology, University of Minnesota, St. Paul Ramsey Hospital, St. Paul, MN 55101 **Anticonvulsant action of diazepam: increase of cortical postsynaptic inhibition.** Epilepsia. 18(1):117-120, 1977.

The action of intravenously administered diazepam on postsynaptic inhibition was studied in cat motor cortex. The efficacy of postsynaptic inhibition of pyramidal tract cells was measured as the ability to suppress action potential generation. Diazepam increased the suppression of action potentials by inhibition. This effect may explain the anticonvulsant action of diazepam. 18 references. (Author abstract)

003247 Raiteri, Maurizio; del Carmine, Renata; Bertollini, Alberto; Levi, Giulio. Istituto di Farmacologia, Universita Cattolica, Via Pineta Sacchetti 644, I-00168 Rome, Italy **Effect of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine, and 5-hydroxytryptamine.** European Journal of Pharmacology (Amsterdam). 41(2):133-143, 1977.

The interaction of sympathomimetic amines with the transport of 3H-noradrenaline (3H-NE), 3H-dopamine (3H-DA), and 3H-5-hydroxytryptamine (3H-5-HT) was investigated in rat hypothalamic 3H-NE and striatal 3H-DA and 3H-5-HT synaptosomes. Modifications in the phenylethylamine structure led to the following changes in activity towards biogenic amine uptake and release: 1) the introduction of a beta-OH group led to compounds less active in inhibiting uptake and stimulating release of 3H-NE, 3H-DA, and 3H-5-HT, with the exception of 3H-NE release, which was stimulated more by unlabeled 1-NE than by DA; 2) the introduction of phenolic --OH groups always led to compounds which were stronger uptake inhibitors and releasers of the three biogenic amines; 3) the alpha-methylation increased the potency towards uptake inhibition and release stimulation, with the exception of the 3H-NE release: in fact, the releasing activity of phenylethylamine was suppressed by alpha-methylation; 4) the introduction of a --Cl group in the para position selectively potentiated the effects on 3H-5-HT uptake and release and generally depressed those on catecholamine transport. 33 references. (Author abstract modified).

003248 Rastogi, Ram B.; Agarwal, Ram A.; LaPierre, Yvon D.; Singhal, Radhey L. Departments of Pharmacology and Psychiatry, Faculty of Medicine, University of Ottawa, Ottawa, Canada **Effects of acute diazepam and clobazam on spontaneous locomotor activity and central amine metabolism in rats.** European Journal of Pharmacology (Amsterdam). 43(2):91-98, 1977.

A study of the effects of acute administration of diazepam and clobazam on spontaneous locomotor activity and central amine metabolism in rats is reported, in which tyrosine hydroxylase activity in the pons medulla area was enhanced by 17% 2 hours after a single injection of diazepam, 10mg/kg. No effect was found on tyrosine hydroxylase in striatum, a region abundant in dopaminergic nerve endings. Diazepam elevated the levels of norepinephrine and dopamine in several brain regions. However, it decreased the concentration of homovanillic acid and augmented that of 3,4-dihydroxyphenylacetic acid, an intraneuronal metabolite of dopamine, suggesting that this antianxiety agent reduced the neuronal release of dopamine and possibly norepinephrine. The enhanced activity of tyrosine hydroxylase in pons medulla appears to reflect a specific compensatory response to the postulated low levels of catecholamines in the synaptic clefts. Acute diazepam treatment decreased tryptophan hydroxylase activity and the endogenous levels of its substrate, tryptophan in midbrain region; however, the levels of 5-hydroxytryptamine and

its metabolite 5-hydroxyindoleacetic acid were markedly increased in hypothalamus midbrain and pons medulla, suggesting that diazepam decreased the synthesis as well as the neuronal release of 5-hydroxytryptamine. Clobazam (10mg/kg) which is a 1,5-benzodiazepine, failed to exert any significant effect on behavioural activity and catecholamine metabolism although like diazepam, it also enhanced the levels of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid. It is suggested that whereas diazepam may exert its behavioral suppresent effect by reducing the turnover of catecholamine, its anxiolytic action may be related to decreased turnover of brain 5-hydroxytryptamine. 28 references. (Author abstract)

003249 Rastogi, Ram B.; Singhal, Radhey L. Department of Pharmacology, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada **Lithium: modification of behavioral activity and brain biogenic amines in developing hyperthyroid rats.** Journal of Pharmacology and Experimental Therapeutics. 201(1):92-102, 1977.

The effect of lithium was studied in developing hypterthyroid rats to delineate its modification of behavioral activity and brain biogenic amines. Daily treatment of neonatal rats with L-triiodothyronine for 30 days increased locomotor activity as well as the synthesis and presumably, release of brain norepinephrine, dopamine and 5-hydroxytryptamine. Administration of lithium carbonate (60mg/kg) to normal rats for 10 days, beginning from the 20th day of age, produced no significant effect, significantly decreased the observed increase in spontaneous locomotor activity in L-triiodothyronine treated rats. Lithium treatment in normal rats increased the activity of striatal tyrosine hydroxylase, but produced no significant effect on the endogenous levels of norepinephrine and dopamine in several discrete brain regions examined. In contrast to the effects seen in normal rats, administration of lithium in L-triiodothyronine treated animals significantly decreased tyrosine hydroxylase as well as dopamine and its metabolite, 3,4-dihydroxyphenylacetic acid, suggesting that this antimanic drug reduced the synthesis and turnover of dopamine. However, the steady state levels of norepinephrine were raised in hypothalamus, pons medulla, midbrain and striatum of lithium treated hyperthyroid rats. As seen in normal animals, lithium in L-triiodothyronine treated rats increased tryptophan, tryptophan hydroxylase and 5-hydroxyindoleacetic acid. The results suggest that the suppressed behavioral activity seen in lithium treated hyperthyroid rats may be associated with decreased synthesis of norepinephrine and dopamine in the brain. 50 references. (Journal abstract modified)

003250 Richardson, T. L.; Miller, J. J.; McLennan, H. Department of Physiology, Faculty of Medicine, University of British Columbia, Vancouver, B.C. V6T 1W5, Canada **Mechanisms of excitation and inhibition in the nigrostriatal system.** Brain Research (Amsterdam). 127(2):219-234, 1977.

The extracellular responses of neurones in the neostriatum following single pulse stimulation of the substantia nigra were investigated in urethane anesthetized rats following administration of a number of dopamine antagonistic drugs. Low intensity stimulation evoked single large amplitude spikes while higher intensities elicit a high frequency burst of small amplitude spikes or waves. When spontaneous or glutamate induced large spikes are recorded, nigral stimulation causes their inhibition coincidentally with the development of a burst. If the burst is prevented, the inhibitory response disappears. Both the nigral evoked inhibition and burst response are unaffected by iontophoretically or systemically administered antagonists of dopamine or by chemical lesions of the dopamine containing nigral neurones. The monosynaptic activation of large amplitude striatal neurones, which could also be identified antidromically by stimulation of the globus pallidus, was reversibly blocked by dopamine antagonists. It is concluded that the burst responses are induced through the antidromic excitation of striatonigral axons within the striatum; that the striatal neurones thus activated are inhibitory interneurones and that the dopamine containing neurones of the nigra make excitatory synaptic contact with a population of striatal output cells, some of which at least project to the globus pallidus. 47 references. (Author abstract)

003251 Richter, Judith A.; Waller, Marshall B. Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, IN 46202 **Effects of pentobarbital on the regulation of acetylcoholine content and release in different regions of rat brain.** Biochemical Pharmacology (Oxford). 26(7):609-615, 1977.

The effects of pentobarbital on tissue levels of acetylcholine (ACh) and on the release of this transmitter from different regions of rat brain were investigated in order to test the hypothesis that increased levels of ACh are the result of the inhibition of ACh release and a subsequent accumulation of the transmitter. Pentobarbtial administered to rats in vivo increased the levels of ACh in the cerebral cortex, striatum, hippocampus, and pons medulla, but not in the midbrain or cerebellum. When pentobarbtial was tested in vitro, the drug inhibited potassium stimulated ACh release from all regions. In vitro, potassium stimulation enhanced ACh release from both cerebral cortex and midbrain but decreased tissue levels of ACh only in the cerebral cortex. Pentobarital inhibited potassium stimulated ACh release from both cerebral cortex and midbrain but increased tissue ACh only in the cerebral cortex. It is suggested that the regulation of ACh synthesis and release is different in the two brain regions and that pentobarbital can inhibit ACh release without necessarily causing a concomitant rise in ACh tissue levels. 44 references. (Author abstract modified)

003252 Riffee, William H.; Gerald, Michael C. College of Pharmacy, University of Texas at Austin, Austin, TX 78712 **The effects of chronic administration and withdrawal of dextroamphetamine on seizure threshold and endogenous catecholamine concentrations and their rates of biosynthesis in mice.** Psychopharmacology (Berlin). 51(2):175-179, 1977.

A study was carried out in mice to determine: 1) whether chronic administration of dextroamphetamine results in tolerance to pentylenetetrazol (PTZ) induced seizure threshold; 2) whether physical dependence to amphetamine could be demonstrated; and 3) the effects of chronic administration of amphetamine and its withdrawal on the endogenous concentrations of noradrenaline (NA) and dopamine (DA) and the rates of biosynthesis of NA and DA. After 7 days of amphetamine administration, tolerance developed only to the decrease in PTZ seizure threshold. After abrupt withdrawal of 2.5mg/kg doses, seizure threshold was decreased; after abrupt withdrawal of 15mg/kg dose, seizure threshold was increased. After acute and chronic administration of 2.5mg/kg amphetamine, endogenous concentrations of whole brain DA were increased and returned to normal levels during the withdrawal period; endogenous norepinephrine (NE) levels were unchanged. After amphetamine withdrawal, the rates of synthesis of DA and NA were increased. Single 15mg/kg doses of amphetamine decreased endogenous levels of NA and DA; with chronic administration, DA levels returned to normal but NA levels remained slightly decreased. The rates of synthesis

of DA and NA were increased by acute and chronic administration and returned to normal after withdrawal. The rebound reversal in seizure threshold after dextroamphetamine withdrawal suggests an abstinence syndrome that may be interpreted as evidence for the development of physical dependence to the drug. 16 references. (Author abstract modified)

003253 Riffee, William H.; Gerald, Michael C. College of Pharmacy, University of Texas, Austin, TX 78712 **Acute and chronic effects of (-)-amphetamine on seizure threshold and brain catecholamines in mice.** Biochemical Pharmacology (Oxford). 26(8):799-801, 1977.

Acute and chronic effects of negative amphetamine on seizure threshold and brain catecholamines were studied in mice with emphasis on correlation of effects with drug induced alterations in endogenous concentrations of brain norepinephrine and dopamine and their rates of biosynthesis. Two dose levels of negative amphetamine were compared, noting that 4mg/kg elevated seizure threshold after acute administration and 15mg/kg was ineffective in the test system. Chronic administration of negative amphetamine for 7 days showed that at a dosage of 4mg/kg the seizure threshold was attenuated, but at a dosage of 15mg/kg the seizure threshold was unchanged. 22 references.

003254 Roberge, A. G. Lab. de Neurobiologie, Dept. de Biochimie, Faculte de Medecine, Universite Laval, Quebec G1K 7P4, Canada **Differentiation in brain and liver DOPA/5HTP decarboxylase activity after L-DOPA administration with or without pyridoxine in cats.** Journal of Neurochemistry (Oxford). 28(3):479-485, 1977.

L-DOPA was administered alone or with pyridoxine to cats to compare brain and liver 5-hydroxytryptophan decarboxylase (DOPA/5-HTP decarboxylase) activity in vivo and in vitro. Pyridoxine given for 7 consecutive days did not modify the content of dopamine, noradrenaline, and serotonin in the neostriatum of the brain 3, 6 and 18 h after the last dose, but significantly increased DOPA/5-HTP decarboxylase activity in both the neostriatum and liver. The administration of L-DOPA and pyridoxine together for 7 days increased DOPA/5-HTP decarboxylase activity in the brain to the same extent as did L-DOPA and pyridoxine given individually. Liver DOPA/5-HTP decarboxylase activity remained normal when both drugs were administered together, however it decreased significantly after L-DOPA administration for 7 days but not after pyridoxine treatment. In cats under treatment with L-DOPA for 7 days, actinomycin D given for the final 3 days prevented the increased DOPA/5-HTP decarboxylase activity induced by L-DOPA in the neostriatum and mesencephalon but had no effect on the enzymatic activity in the liver. These findings appear to indicate that differences exist between brain and liver DOPA/5-HTP decarboxylase activity in vivo. In addition, denatured supernatant from livers of animals treated with L-DOPA contained a dialysable compound which inhibits DOPA/5-HTP decarboxylase activity in the supernatant from livers of untreated cats. In animals who received pyridoxine along with L-DOPA, no such inhibitor was found. It is suggested that these results may explain the mechanism by which L-DOPA exerts its beneficial effects and why pyridoxine administered with L-DOPA reduces the therapeutic effectiveness of L-DOPA in Parkinson's disease. These findings were consistent with the possibility that a tetrahydroisoquinoline derivative formed in vivo in the liver after L-DOPA therapy for 7 days might affect DOPA/5-HTP decarboxylase activity in the liver but not in brain. 52 references. (Author abstract modified)

003255 Rommelspacher, H.; Strauss, S.; Rehse, K. Institute of Neuropsychopharmacology, Free University of Berlin, Ulmenallee 30, D-1000 Berlin 19, Germany **Structure activity relations for the inhibition of serotonin uptake by beta-carbolines into synaptosomes from rat brain.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R54, 1977.

A study of the structure/activity relationships for the inhibition of serotonin (5-HT) uptake by beta-carbolines into synaptosomes from rat brain is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. The effects of several substituted beta-carbolines on the high affinity uptakes of serotonin 5-HT, noradrenaline (NA), dopamine (DA), gamma-aminobutyric acid (GABA), and choline into rat brain synaptosomes were investigated. The chlor substituted derivatives were the most active inhibitors of 5-HT uptake, followed by unsubstituted beta-carbolines, the 6-methoxy derivaties, and the 6-hydroxy derivatives. Other derivatives were less active. NA uptake was slightly less affected than that of 5-HT, and inhibition of DA, GABA, and choline uptake were also observed. The results support the notion that beta-carbolines inhibit the high affinity uptake of putative neurotransmitters and that this effect is dependent on the chemical structure. (Author abstract modified)

003256 Rose, D.; Horn G. University of Bristol, Department of Anatomy, Medical School, Bristol BS8 1TD, England **Effects of LSD on the responses of single units in cat visual cortex.** Experimental Brain Research (Gottingen). 27(1):71-80, 1977.

The effects of intravenous doses of LSD on the activity of single neurons in the primary visual cortex was studied in cats anaesthetized with urethane. Cells were stimulated with a single bar of light moved over the receptive field and orientation tuning was assessed quantitatively before and after administration of the drug. Changes in neuronal activity were compared with those observed in a control sample of cells recorded when the cats were given no drug. LSD increased the responsiveness of some cells to visual stimuli and decreased that of others, but some cells were not affected. The changes in responsiveness were dose dependent; the larger doses of the drug tended to depress the responses and the smaller doses to enhance them. The effects appeared earlier in complex cells than in simple cells. Changes in spontaneous activity, direction selectivity, and orientational properties were found in some cells. 15 references. (Author abstract)

003257 Rosenfeld, J. Peter; Holzman, Bradley S. Cresap Neuroscience Laboratory, Departments of Psychology and Psychiatry, Northwestern University, Evanston, IL 60201 **Differential effect of morphine on stimulation of primary versus higher order trigeminal terminals.** Brain Research (Amsterdam). 124(2):367-372, 1977.

Antinociceptive effects of morphine on consequences of spinal trigeminal complex stimulation were differentially compared with effects of morphine on stimulation of sites in the ventrobasal complex in thalamus where the secondary (and higher order) ascending trigeminothalamic neurons synapse with higher order cells, hypothesizing that opiates would elevate thresholds for aversive stimulation at the spinal trigeminal nucleus but not at levels of the neuraxis upstream from the site of descending inhibitory action. Male Holtzman albino rats were implanted with stimulating electrodes aimed at the spinal trigeminal tract and at the medial portion of the ventrobasal complex. Brain stimulation produced three types of effects: motoric/nonaversive, aversive/motoric, and aversive.

Two passive avoidance procedures were used to be compatible with the species specific consequences of trigeminal aversion (subjectively defined aversive and step down situation). Data obtained indicated the failure of opiates to alter thresholds for aversive brain stimulation and demonstrated evolution of lateral diencephalic sites. Data support a descending inhibitory mechanism or direct action at or distal to the primary afferent terminal region. 8 references.

003258 Rosman, N. Paul; Malone, Michael J. no address **Reversal of delayed myelinogenesis in the fetal alcohol syndrome.** Neurology. 27(4):369, 1977.

At a meeting of the American Adademy of Neurology in Atlanta, GA in april, 1977, the reversal of delayed myelinogenesis in the fetal alcohol syndrome was investigated in rats. Pregnant rats were placed on a liquid diet, with or without ethanol, and the newborn rats were sacrificed between 12 and 40 days. The newborns did not differ in body or brain weight and the brains showed no macroscopic alterations, but microscopic study showed a striking delay in myelinogenesis in the ethanol group. There were no differences in brain phospholipid, cholesterol, or glycolipid, but lipid soluble protein, an important marker of myelinogenesis, was reduced in the ethanol group. In a crossover study, half the offspring born to control mothers were fed the ethanol diet at weaning, and half those born to ethanol mothers were fed the control diet. At 28 days, there were no differences among the 4 groups. At 32 and 40 days, the animals exposed to ethanol during gestation or postnatally showed a clear reduction in brain lipid soluble protein. By 60 days, however, there again were no differences between the 4 groups. Early alcohol exposure appears to have an adverse but reversible effect on the accumulation of brain lipid soluble protein.

003259 Roth-Schechter, B. F.; Mandel, P. Centre de Neurochimie du CNRS, 11 rue Humann, F-67085 Strasbourg, Cedex, France **Preferential neurotoxicity of pentobarbital on nerve and glial cells in culture.** Experientia (Basel). 33(5):627-629, 1977.

The effect of pentobarbital was studied in a mixed population of nerve and glial cells dissociated from brains of 7 day chick embryos and maintained in culture. Pentobarbital-Na was added in various concentrations. The neuronal density was monitored by counting of neurons; neuronal identity was established by staining for Nissl Bodies and a cetylcholinesterase. Over aculture period of 3 weeks, it was found that the barbiturate exerts a preferential dose dependent cytotoxic effect on neurons. 12 references. (Author abstract)

003260 Roy, Edward J.; Maass, Christie A.; Wade, George N. Rockefeller University, New York, NY 10021 **Central action and a species comparison of the estrogenic effects of an antiestrogen on eating and body weight.** Physiology & Behavior. 18(1):137-140, 1977.

Adult female gerbils (N=30) and adult female rats (N=10) were treated with ethamoxytriphetol (MER-25), an antiestrogen, to assess central action between species on eating behavior and bodyweight. The antiestrogen MER-25 was itself fully estrogenic on eating and bodyweight. In rats, MER-25 decreases food intake when implanted in the same hypothalamic areas in which estradiol decreases food intake. In gerbils, both estradiol benzoate and MER-25 cause increased food intake and bodyweight. 21 references. (Author abstract modified)

003261 Saban, Ricardo; De Moraes, Sergio. Therapeutics Laboratory, Faculty of Veterinary Medicine, University of Sao Paulo, Sao Paulo, Brazil **Noradrenergic supersensitivity in the rat vas deferens during barbital withdrawal.** European Journal of Pharmacology (Amsterdam). 43(2):195-198, 1977.

Noradrenergic supersensitivity in the rat vas deferens during barbital withdrawal was investigated. Three days' withdrawal from long-term barbital administration results in a shift to the left and increase in the maximum response of the concentration effect curve to norepinephrine in the isolated rat vas deferens. The maximum response to carbachol and potassium was also increased without a leftward displacement of the concentration effect curves. This specific increase in sensitivity to norepinephrine could indicate an adaptive alteration of the adrenoreceptors of the rat vas deferen (receptor supersentivity) as has been proposed for supersensitivity in the central nervous system during withdrawal from neuroleptics and barbiturates. 10 references. (Author abstract)

003262 Sabelli, H. C.; Diamond, B. I.; May, J.; Havdala, H. S. Department of Anesthesiology and Psychiatry, Mount Sinai Hospital, Chicago, IL 60608 **Differential interactions of phenobarbital and pentobarbital with beta-adrenergic mechanisms in vitro and vivo.** Experimental Neurology. 54(3):453-466, 1977.

The differential interactions of phenobarbital (PH) and pentobarbital (PE) with beta-adrenergic mechanisms were studied in vitro and in vivo. In isolated frog nerves, the spike amplitude lowering effect PE was augmented by L-epinephrine and blocked by the beta-adrenergic blockers, sotalol and propranolol, or by the alpha-adrenergic agent phentolamine. The drug interactions, as well as other interactions with calcium (CA) and with the dibutyryl derivative of cyclic adenosine monophosphate, suggest that PE activates axonal beta-adrenergic mechanisms. In contract, the effects of PH and procaine were antagonized by L-epinephrine. CA appears to be an important second messenger for the effects of epinephrine on barbiturate actions. The effect of PH differed from that of procaine in not being CA dependent. The results indicate that PE and PH affect electrically excitable membranes in a specific manner, different from that of nonspecific membrane stabilizers and from each other. In vivo experiments (mouse maximal electroshock seizures) showed that the beta-blockers also interacted with PE, but not with PH. 28 references. (Author abstract modified)

003263 Samuel, David. Isotope Department, Weizmann Institute of Science, Rehovot, Israel **The measurement of biogenic amine turnover using osygen-18.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 95-104).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December, 1975, a method for measuring the turnover of biogenic amines using oxygen-18 is described and the results of preliminary studies in rats, mice, and baboons using this technique are reported. Causing test animals to breathe air in a specially designed apparatus in which the circulating oxygen is gradually replaced by highly enriched oxygen-18 results in an extremely stable oxygen-18 label being introduced into the meta-hydroxyl group of brain dopamine (DA) and norepinephrine and the 5-hydroxy group of serotonin (5-hydroxytryptamine). This label is retained throughout all the catabolic processes which produce the various metabolites of these amines. The labeled amines and their

metabolites are then measured by mass fragmentography. The technique has been used to measure the labeled amines and their metabolites in whole brain homogenates of the rat and the blood, urine, and cerebrospinal fluid of the baboon; the rate of DA turnover in the corpus striatum of the rat; and the effects of various drugs, including chlorpromazine, alphamethylparatyrosine, parachlorophenylalanine, and pentobarbital, on biogenic amine turnover and concentration. 14 references.

003264 Saner, Alphonse; Pletscher, Alfred. Research Division, F. Hoffman-La Roche & Co. Ltd., Basel, Switzerland **Increase of striatal dopamine turnover by drugs: interference with granular storage or receptor blockade?** European Journal of Pharmacology (Amsterdam). 42(2):155-160, 1977.

The question of whether drugs that increase striatal dopamine turnover act by interference with granular storage or receptor blockade was studied in rats. Apomorphine completely antagonized the reserpine induced enhancement of the striatal 3,4-dihydroxyphenylalanine (dopa) accumulation seen after administration of the decarboxylase inhibitor 3-hydroxybenzylhydrazine (NSD 1015) (HBD). Reserpine-like drugs: Ro-4-1284(2-hydroxy-2-ethyl-isobtyl-9,10-dimethoxy-1,2,3,4,6,7-hexahyd o-11bH-benzo(a)quinolizine HCl and Ro-4-9040(bis-(3,4-dichlorophenethyl) amine methanesulfonate) markedly enhanced the striatal dopa accumulation due to HBD in normal animals but not in rats treated with reserpine plus apomorphine. Haloperidol enhanced the striatal dopa accumlation to a similar extent in normal and in reserpine plus apomorphine treated animals. Chlorpromazine also enhanced striatal dopa accumulation in both types of animals, but its potency was somewhat higher in the normal rats. Reserpinized animals treated with apomorphine appear to be useful models for differentiating whether a drug enhances striatal dopamine turnover by interference with granular dopamine storage or by blockade of dopamine receptors. The latter seems to be the main mechanism of action of neurotropic drugs. 14 references. (Author abstract modified)

003265 Sangiah; Subbiah; Domino, Edward F. Department of Pharmacology, Lafayette Clinic, Detroit, MI 48207 **In vitro studies of some chlorpromazine metabolites as potential N-methyltransferase inhibitors.** Research Communications in Chemical Pathology and Pharmacology. 16(2):389-392, 1977.

The inhibition of rabbit lung N-methyltransferase activity by a series of chlorpromazine metabolites was examined in vitro. The hydroxylated metabolites were found to be more effective, with the 7, 8-dioxy derivatives the most potent. Various chelating agents had no effect, suggesting that the inhibitory effects of the hydroxy metabolietes were not due to divalent cation chelation. 10 references. (Author abstract modified)

003266 Sasa, Masashi; Munekiyo, Katsunori; Osumi, Yoshitsugu; Takaori, Shuji. Department of Pharmacology, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan **Attenuation of morphine analgesia in rats with lesions of the locus coeruleus and dorsal raphe nucleus.** European Journal of Pharmacology. 42(1):53-62, 1977.

The nociceptive reflex and attenuation of morphine analgesia in rats with lesions of the locus coeruleus (LC) and dorsal raphe nucleus (DR) was studied using the hind paw stimulation test. The stimulation threshold was significantly increased in rats with bilateral destruction of LC and was reduced after lesion of DR. LC lesions produced a selective lowering of noradrenaline (NA) content in the forebrain, while DR lesions resulted in a reduction in serotonin levels. Lesioning both LC and DR significantly reduced both NA and serotonin contents even when the stimulation threshold was not altered. Morphine produced a significant and dose dependent elevation of the stimulation threshold in sham operated animals, while morphine analgesia was almost completely inhibited by destruction of LC, DR and both the nuclei. These results imply that a depression of LC mediated noradrenergic tone results in a decreased sensitivity to painful stimuli, whereas a reduction of raphe derived serotonergic tone produces the opposite effect against LC. It is suggested, however, that both of these monoamines from the LC and DR are necessary for the analgesic effect of morphine. 33 references. (Author abstract modified)

003267 Schaefer, A.; Seregi, A.; Komlos, Marta. Institute of Experimental Medicine, Hungarian Academy of Sciences, 1450 Budapest 9, P.O.B. 67, Hungary **Inhibition of the sodium and potassium-stimulated adenosine triphosphatase activity during autooxidation of apomorphine.** Journal of Pharmacy and Pharmacology (London). 29(2):117-118, 1977.

The inhibition of sodium adenosine triphosphatase (Na+ATPase) and potassium adenosine triphosphotase (K+ATPase) activity during autooxidation of apomorphine in rat brain preparations. Determination of the ATPase activity was based on the measurement of inorganic phosphate liberated from ATP. Incubations were carried out and the enzyme activities were calculated. The ATPase activity of the partially purified Na+,K+-ATPase preparation, isolated from rat brain, was strongly inhibited in the presence of various amounts of apomorphine. When experiments were made on microsomal preparations rich in magnesium stimulated adenosine triphosphatase (Mg2+ATPase), the Mg2+-ATPase activity was only slightly inhibited. The strong inhibitory effect of apomorphine on Na+,K+-ATPase activity was eliminated by the presence of ascorbic acid or cysteine in the incubation mixture. It is suggested that the inhibition of Na+,K+-ATPase activity might occur following the oxidation of apomorphine, or, as a result of the free radical intermediates formed during oxidation. 19 references.

003268 Scheel-Kruger, J.; Cools, A. R.; Honig, W. Psychopharmacological Research Laboratory, Dept. E., St. Hans Mental Hospital, DK-4000 Roskilde, Denmark **Muscimol antagonizes the ergometrine-induced locomotor activity in nucleus accumbens: evidence for a GABA-dopaminergic interaction.** European Journal of Pharmacology (Amsterdam). 42(3):311-313, 1977.

The effect of muscimol (MUS) on the ergotamine (ERG) induced locomotor activity in the rat nucleus accumbens was studied. MUS, a potent and specific gamma-aminobutyric acid (GABA) agonist was injected locally after ERG, a dopamine stimulant, was injected into the nucleus accumbens. MUS induced a complete and highly significant inhibition of ERG motility for up to 3 hr; the rats were calm and silent without behavioral stimulant effects. In the ERG/MUS group, a locomotor response was seen 3 to 4 hrs after ERG that did not differ from that of the ERG placebo group. MUS (10 nanograms) injected bilaterally into naive rats induced no behavioral changes, whereas MUS (100 nanograms) induced sedation increasing to catalepsy 1 hr after the injection. The results provide evidence for a GABA mediated modulatory influence on dopaminergic mechanisms in the nucleus accumbens.

003269 Schocker, W.; Schulz, J. Pharmazeutisches Institut der Universitat, Auf der Morgenstelle 8, D-7400 Tubingen,

Germany **Changes of the formation of cAMP and the content of noradrenaline (NA) in rat brain after treatment with imipramine (IMI), reserpine (RES) and alpha-methyl-p-tyrosine (a!pha-MPT).** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R14, 1977.

A study of the effects of imipramine (IMI), reserpine (RES), and alpha-methyl-paratyrosine (AMPT), alone or in combination, on noradrenaline (NA) content and on the NA stimulated formation of cyclic adenosine monophosphate (cAMP) in rat cerebral cortex is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany, in March 1977. IMI reduced NA levels and NA stimulated cAMP formation. AMPT decreased NA levels but did not significantly alter NA stimulated cAMP formation. RES reduced NA content and enhanced NA stimulated cAMP formation after 6 da of treatment but the enhanced cAMP response was not apparent after 10 da of treatment. Administration of AMPT concomitantly with IMI inhibited the changes seen after IMI alone. Administration of RES concomitantly with IMI resulted in a large reduction of the NA stimulated cAMP formation and in partial inhibition by IMI of the reduction in NA levels produced by RES alone. Because the antidepressant activity of IMI is not impaired in patients treated with IMI and AMPT, it is suggested that the hypothesis that antidepressant treatment is related to a reduced formation of cAMP in NA neurones should be reevaluated. (Author abstract modified)

003270 Schoenfeld, W. N.; Kadden, R. M.; McMillan, J. C. Research Laboratory, Building 7, Room 19, FDR VA Hospital, Montrose, NY 10548 **Effectiveness of atrial pacing in Macaca mulatta as a function of pacing pulse intensity: modification by atropine and propranolol.** Pavlovian Journal of Biological Science. 12(1):32-40, 1977.

The functional relationship between heartrate, under atrial pacing, and the intensity of pacing pulses, was determined for intensities ranging from well below the complete heartrate capture threshold to suprathreshold intensities in four rhesus monkeys. A separate capture intensity function was determined for each of the pacing frequencies 180, 240, 300 and 360 pulses per min, and then used to evaluate the effects of propranolol hydrochloride and atropine sulfate on atrial pacing. Propranolol resulted in an increase in the amount of current (mA) required to achieve a given degree of cardiac capture, whereas atropine resulted in a decrease. These shifts in the capture intensity functions along the intensity axis were possibly caused by drug antagonism of beta-adrenergic and cholinergic receptors, respectively, although the effects might also have been due to modifications of the electrical responsivity of the cardiac muscle, independently of the neural blockade. 8 references. (Author abstract)

003271 Schorderet, Michel. Department of Pharmacology, School of Medicine, CH-1211, Geneva 4, Switzerland **Lithium inhibition of cyclic AMP accumulation induced by dopamine in isolated retinae of the rabbit.** Biochemical Pharmacology (Oxford). 26(2):167-170, 1977.

The process of lithium inhibition of dopamine induced cyclic adenosine monophosphate (AMP) accumulation in isolated retinae of the rabbit was examined. The results of the experiment indicate that more than 50% inhibition of the dopamine effect on cyclic AMP accumulation was obtained when 5mM lithium was present. Complete inhibition was achieved in the presence of 50mM lithium. It is concluded that one of the cellular effects of lithium is a specific inhibition of dopamine sensitive adenylate cyclase. 9 references.

003272 Schulz, R.; Laschka, E.; Blasig, J.; Herz, A. Department of Neuropharmacology, Max Planck Institute for Psychiatry, Kraeplinstrasse 2, D-8000 Munchen 40, Germany **Altered sensitivity of the rat central nervous system to neurotransmitters during precipitated morphine-withdrawal.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R53, 1977.

A study of altered sensitivity of the rat central nervous system to neurotransmitters during naloxone precipitated morphine withdrawal is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft held in Mainz, Germany in March 1977. Chronically morphinized rats were challenged with intracerebroventricularly injected dopamine (DA), apomorphine, noradrenaline, clonidine, and serotonin (5-hydroxytryptamine) after naloxone induced jumping had ceased. DA and apomorphine reinduced jumping in a dose dependent manner. No jumping or other withdrawal signs were elicited by any of the compounds in naive or tolerant/dependent rats not challenged with naloxone. In an attempt to localize the site of action of apomorphine, the spread of the drug was restricted by a plug inserted into the aqueduct mesenceph. Apormophine caused jumping when injected into the anterior part of the restricted ventricular system but not when injected into the fourth ventricle. When naloxone was used to terminate opiate action, only weak withdrawal signs were obtained when the drug was given in the anterior part of the ventricular system, while jumping was precipitated when naloxone was administered into the fourth ventricle. It is suggested that the site of action of apomorphine in reinitiating naloxone induced jumping does not coincide with the site of action at which naloxone acts to precipitate this sign. (Author abstract modified)

003273 Schulze, G.; Tetzner, M.; Topolinski, H. Institute of Neuropsychopharmacology, Free University Berlin, Ulmenallee 30, D-1000 Berlin 19, Germany **The influence of lesions in the diencephalon and of drugs on the thermoregulatory behaviour of rats.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R56, 1977.

Studies of the influence of lesions in the diencephalon and of phentolamine on the thermoregulatory behavior of rats are reported in a paper given at the 18th spring meeting of the Deutsche Pharmaokologiche Gesellschaft held in Mainz, Germany, in March 1977. Bilateral lesions of the anterior hypothalamus diminish autonomic thermoregulatory capacity so that behavioral thermoregulation becomes important for the maintenance of body temperature. Contrary to control animals, lesioned rats work in cold surroundings for exogenous heat in order to stabilize their ambient temperature. Response rates are dependent on the preset ambient temperature. Without this behavioral substitution, body temperature decreases. In unlesioned animals, phentolamine produces hypothermia and an increase of response rate for heat reinforcement in a dose dependent manner. In lesioned animals, the effects of the drug are additive to the effects of the lesion, so that the response rate increases. It is suggested that the lesioned brain region is not involved in mediating the hypothermic effect of the drug. (Author abstract modified)

003274 Schutz, H.; Krieglstein, J.; Rieger, H. Institut fur Pharmakologie und Toxikologie im FB Pharmazie, Deutschhausstrasse 17a, D-355 Marburg, Germany **Comparison of the effects of chlorpromazine and some of its metabolites on the isolated perfused rat brain.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R57, 1977.

A study comparing the effects of chlorpromazine, monodesmethylchlorpromazine, didesmethylchlorpromazine, and chlorpromazine-N-oxide on the electroenephalogram (EEG) and on dopamine (DA) metabolism in the isolated perfused rat brain is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft held in Mainz, Germany, in March 1977. Chlorpromazine-N-oxide was the most potent compound in increasing the EEG amplitude, followed by chlorpromazine, monodesmethyl-chlorpromazine, and didesmethylchlorpromazine in descending order of potency. A significant increase of the homovanillic acid (HVA) content in the striatum was found after chlorpromazine-N-oxide but not after the other compounds tested. It is suggested that chlorpromazine-N-oxide may be more active than its parent compound chlorpromazine. (Author abstract modified)

003275 Scriabine, Alexander; Stavorski, John M. Merck Institute for Therapeutic Research, West Point, PA 19486 **Effects of phentolamine, phenoxybenzamine and desipramine on clonidine-induced blockade of cardiac acceleration in the dog.** European Journal of Pharmacology (Amsterdam). 42(1):63-69, 1977.

The effects of phentolamine (PT), phenoxybenzamine (PB), and desipramine (DP) on clonidine (CL) induced blockade of cardiac acceleration was studied in dogs. CL reduced cardiac acceleration induced by low frequency electrical stimulation of cardiac sympathetic nerve fibers in anesthetized and vagotomized dogs. This effect of CL was abolished by short periods of high frequency electrical stimulation. The inhibitory effect of CL was observed with 10 as well as with 90 sec period of electrical stimulation. Pretreatment with PT, PB and DP antagonized the CL induced inhibition as shown by a dose dependent shift of the dose response regression lines of CL to the right. PT was more potent than PB or DP. The onset of action of the alpha-adrenergic blocking drug and DP was immediate and lasted in excess of the duration of the experiment (70 min). At the doses used, PT, PB, and DP did not have any significant effect on the heartrate per se. The results suggest the presence of alpha-adrenoceptors at the peripheral sympathetic nerve endings in the dog. 15 references.

003276 Segal, Menachem; Sandberg, David. Isotope Department, Weizmann Institute of Science, Rehovot, Israel **Analgesia produced by electrical stimulation of catecholamine nuclei in the rat brain.** Brain Research (Amsterdam). 123(2):369-372, 1977.

Adult male rats with electrode implants in the nucleus locus coeruleus (LC) (N=13) and dopaminergic substantia nigra (SN) (N=11) were compared to controls (N=10) to investigate possible correlations between self-stimulation (SS) and analgesia as well as the possibility that the brainstem catecholamine nuclei are involved in pain mechanisms. The analgesic effects of morphine in the three groups were also assessed. No apparent correlations between SS rates and magnitude of analgesia were found in either LC rats or SN rats. It was found that: 1) implantation of stimulating electrodes in the region of LC causes an increase in sensitivity to a painful stimulus, which is counteracted by electrical stimulation; 2) stimulation of SN also reduces the sensitivity to a painful stimulus and acts similarly to morphine as compared to both normal and SN implanted, morphine treated rats; 3) morphine appears to exert a more potent action in LC implanted than in SN or normal rats; and 4) there appears to be a more powerful interaction between morphine and SN stimulation than between morphine and LC stimulation. The results confirm earlier observations and suggest an involvement of both LC and SN in processes related to pain. 15 references.

003277 Shoham-Moshonov, Sandra R.; Weinstock, Marta. Department of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel **Nature of seasonal variation in development of acute tolerance to morphine.** European Journal of Pharmacology (Amsterdam). 43(2):153-161, 1977.

The phenomenon of seasonal variation in the development of acute tolerance to morphine observed during continuous morphine perfusion of the guinea pig ileum was investigated. Acute tolerance is significantly higher in the summer (May/Nov.)than winter (Dec./April). This seasonal variation in development of tolerance does not appear to be related to changes in diet, environmental light or temperature, or to the sensitivity of the ileum to morphine. In the winter, the acetylcholine release from stimulated ilea is lower than in the summer. In addition to inhibiting acetylcholine release, morphine also has a nonspecific blocking effect in the winter. This postjunctional effect could prevent the development of supersensitivity to acetylcholine during continuous morphine treatment so that acute tolerance cannot occur. 21 references. (Author abstract)

003278 Shuster, Louis; Yu, Grace; Bates, Anne. Department of Biochemistry and Pharmacology, Tusts University School of Medicine, 136 Harrison Ave., Boston, MA 02111 **Sensitization to cocaine stimulation in mice.** Psychopharmacology (Berlin). 52(2):185-190, 1977.

Sensitization to cocaine stimulation was studied in mice. Repeated administration of cocaine to B6AF1/J mice increased their running response to 20mg/kg cocaine as much as fourfold over the response to the first injection. After four daily injections, the extent of the increase was proportional to the dose of cocaine that was used for pretreatment. Sensitization persisted for as long as 2 months after the last injection of cocaine. Cocaine pretreated mice did not show an increased running response to either morphine or d-amphetamine. The response to cocaine was increased two-fold by treatment with morphine, and three fold by pretreatment with d-amphetamine. Pretreatment with either imipramine or reserpine did not produce sensitization to cocaine. There was no correlation between cocaine sensitization and whole brain catecholamine levels. There were marked differences in both the running response to cocaine and the extent of cocaine sensitization between the parental strains, C57B1/6J and A/J. Experiments with recombinant inbred lines, derived from C57B1/6By and BALB/cBy mice, suggest that the initial response to cocaine and the development of sensitization are controlled by different genetic determinants. 23 references. (Author abstract modified)

003279 Simantov, Rabi; Snyder, Solomon H. Department of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **Opiate receptor binding in the pituitary gland.** Brain Research (Amsterdam). 124(1):178-184, 1977.

The opiate receptor binding of opiate agonists, opiate antagonists and endogenous opoid peptides in bovine pituitary gland and brain were studied in vitro. Naloxone, diprenorphine, cyclazocine, levallorphan, nalorphine, etorphine, dextrallorphan, codeine, and beta-endorphin had similar binding activities in both brain and posterior pituitary. Morphine, methionine-enkephalin, and leucine-enkephalin were more potent in brain than in pituitary. Sodium ion enhanced the binding of opiate antagonists and reduced the binding of opiate

agonists in both brain and pituitary. Pituitary extracts were shown to compete for opiate receptor binding of radiolabeled naloxone in brain membranes and this binding ability was reduced in the presence of sodium, indicating that pituitary opoid peptides behave like opiate agonists. Striking differences in opoid content and receptor binding were found in the different subdivisions of the pituitary. Pituitary receptors had much greater affinity for the pituitary opoid peptide beta-endorphin than for enkephalins, the opoid peptides of the brain, suggesting that the pituitary receptors are selective for endogenous pituitary opoid peptides. It is concluded that posterior pituitary membranes possess stereospecific opiate receptors whose properties are very similar to those of brain receptors. It is proposed that some of the endocrine effects produced by opiates may be exerted directly via opiate receptors in the pituitary. 27 references. (Author abstract modified)

003280 Smyth, Randolph G.; Tong, Jeffrey H.; D'Iorio, Antoine. Department of Biochemistry, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada **Studies on the depletion of brain amines by m-tyrosine.** European Journal of Pharmacology (Amsterdam). 42(3):267-273, 1977.

The depletion of brain biogenic amines by m-tyrosine (mTyr) was studied in rats. Endogenous levels of dopamine, norepinephrine, and serotonin were reduced approximately 50 percent 1 hr after the administration of L-mTyr. The reductions were blocked by the inhibition of the central dopa decarboxylase with NSD-1055 (4-bromo-3-hydroxybenzyloxyamino phosphate). The D isomer of mTYR also depleted brain monoamines, but to a lesser extent. L-mTyr, m-tyramine, and m-octopamine enhanced the efflux of exogenous labeled monoamines from brain particles in vitro, whereas D-mTyr was completely ineffective. It was concluded that the observed decrease in brain monoamines by L-mTyr may be due to a m-tyramine enhanced release of the amines which are quickly metabolized in vivo. 27 references. (Author abstract modified)

003281 Smythies, John R. Neurosciences Program, University of Alabama in Birmingham, Birmingham, AL 35294 **On the molecular structure of the opiate receptor.** Psychoneuroendocrinology (Oxford). 2(1):71-72, 1977.

An hypothesis of the molecular structure of the opiate receptor in vertebrates is based on two opposed parallel Kusnetsov-Ghokov grids. The receptor in the model consists of a cup which is constructed of 4 pentapeptide segments of protein chain, aligned as 2 beta-pleated (anti-parallel) sheets. The key amino acids are Tyr and Asp on chain A and Asp on chain D. Asp on A is the binding target of the amino group of opiate agonists and antagonists and Asp of D is the target for the phenolic hydroxyl of morphine and similar compounds. The hypothesis suggests that the opiate receptor is immediately adjacent to a sodium binding site. Two conformations of the receptor are described: one promoted by sodium and binding preferentially antagonists and one promoted by sodium lack and binding preferentially agonists.

003282 Snead, O. Carter. no address **Effect of anticonvulsant drug therapy on gamma hydroxybutyrate-induced spike-wave stupor.** Neurology. 27(4):375, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the effects of phenobarbital, ethosuximide, phenytoin, or levodopa pretreatment on gamma-hydroxybutyrate (GHB) induced spike wave stupor was studied in monkeys. GHB produced electroencephalogram (EEG) and behavior changes which closely resembled a petit mal seizure state. A continuous EEG was recorded from scalp electrodes during and after all infusions. Blood samples obtained at varying intervals after the infusions were assayed for GHB and the respective anticonvulsants by gas/liquid chromatography. The baseline responses to GHB consisted of initial low voltage slowing, which progressed to periodic bursts of high-voltage slow waves, often associated with spikes. The animals showed staring with loss of visual following and frequent myoclonic jerks. The depth and duration of stupor, high voltage slowing, and frequency of myoclonic jerks were all made worse by phenytoin, moderately improved by phenobarbital, and markedly improved by ethosuximide. There was little or no change in the levodopa treated monkeys. These studies provide further evidence for the epileptogenic properties of GHB and raise the possibility of the use of this compound as a petit mal seizure model. (Author abstract modified)

003283 Snider, Stuart R.; Snider, Ray S. Dept. of Neurology, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York, NY 10032 **Phenytoin and cerebellar lesions: similar effects on cerebral catecholamine metabolism.** Archives of Neurology. 34(3):162-167, 1977.

The in vivo effects of long-term administration of phenytoin and of cerebellar lesions on catecholamine (CA) metabolism in Sprague-Dawley rats were investigated. Phenytoin 100mg/kg/day for 2 weeks caused an increase in hindbrain norepinephrine (NE) concentration, a slight decrease in forebrain NE concentration, and little change in dopamine (DA) levels. The turnover rates of forebrain DA and NE estimated by synthesis inhibition were increased by 70% and 100% respectively. Surgical lesions of the anterior cerebellar vermis produced similar (but not additive) increases in turnover. It is concluded that long-term phenytoin use stimulates CA metabolism in the forebrain and that this effect may be mediated indirectly by the cerebellar vermis. 42 references. (Author abstract modified)

003284 Snyder, Solomon H. no address **Opiate receptors and internal opiates.** Scientific American. 236(3):44-56, 150, 1977.

The specificity of binding at high affinity binding sites for opiates in cell membrane from rat brain and guinea-pig intestine was investigated by comparing the ability of the active and inactive optical isomers of the opiates to compete with radioactive labeled molecules of naloxone for binding to the receptor. The high concentration of receptors in the limbic system suggests that it is here that opiates exert their euphoria producing actions, and also that one internal opiate-like substance or more may play some role in modifying the emotional component of pain. Polygraph readings (shown) from bioassay apparatus (diagrammed) show that the inhibition of enkephalin, like that of morphine, is blocked by the antagonist naloxone; the similarity of effects suggests that they act at the same receptor. The data suggest that mixed agonist/antagonists developed from the enkephalins might offer promise as nonaddictive analgesics. 5 references.

003285 Sofia, R. D.; Knobloch, L. C.; Harakal, J. J.; Erikson, D. J. Wallace Laboratories, Department of Pharmacology and Toxicology, Half Acre Road, Cranbury, NJ 08512 **Comparative diuretic activity of delta9-tetrahydrocannabinol, cannabidiol, cannabinol and hydrochlorothiazide in the rat.** Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 225(1):77-87, 1977.

In a comparative study of the diuretic activity of delta9-tetrahydrocannabinol (THC), cannabidiol, cannabinol and hydrochlorothiazide (HCT), it was found that orally administered THC produced a dose dependent increase in urine

output in hydrated rats similar in mg/kg potency and magnitude of effect to HCT. Whereas HCT promoted marked excretion of Na+, K+ and Cl- and an increase in the urinary Na+/K+ at all diuretic doses; however, THC had only a slight effect on Na+ and K+ excretion but not Cl- even after the highest dose tested. Hypophysectomy and adrenalectomy abolished the diuretic effect of THC, thus suggesting both central and peripheral sites of action for the diuretic effect of THC. Tolerance to the effect on urine output by THC developed after 15 days of repeated dosing, while urine output and electrolyte excretion remained significantly elevated after 25 days of HCT administration. 17 references. (Author abstract)

003286 Spehlmann, Rainer. no address **The effects of scopolamine on synaptic responses in the intact and the dopamine-depleted caudate nucleus.** Neurology. 27(4):391, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in Aptil, 1977, the effects of the acetylcholine (ACh) antagonist scopolamine on synaptic responses were studied in the intact and the dopamine depleted caudate nucleus of cats to investigate the pathophysiologic mechanisms underlying Parkinson disease. In the intact caudate nucleus, scopolamine blocked the multisynaptic neuronal response to stimulation of the caudate nucleus in the majority of neurons tested. The neuronal responses to the other stimuli were much less affected. This differential block of responses to caudate stimulation is compatible with the idea that ACh acts as a synaptic transmitter of excitatory interneurons in the caudate nucleus. In the dopamine depleted caudate nucleus, significantly larger doses of scopolamine were required to block the responses to caudate stimulation than in the intact caudate nucleus. The proportion of neurons blocked, however, was not significantly changed. This suggests that dopamine depletion of the caudate nucleus leads to an increased ACh liberation. Such an alteration may be the basis for the well known beneficial effects of cholinolytics and the deleterious effect of physostigmine on the signs of Parkinson disease. (Author abstract modified)

003287 Squires, Richard F.; Braestrup, Claus. Research Laboratories, A/S Ferrosan, Sydmarken 1-5, 2860 Soeborg, Denmark **Benzodiazepine receptors in rat brain.** Nature (London). 266(5604):732-734, 1977.

Experiments were performed which show that a group of psychoactive drugs, the benzodiazepines, bind to specific receptors on the membranes of rat brain cells, suggesting that there may be an unknown endogenous neurotransmitter which is the natural ligand for the benzodiazepine receptor. Displacement potencies of the benzodiazepines correlate with pharmacological effects predictive of anxiolytic activity. The exact mechanisms by which benzodiazepines exert their characteristic pharmacological and clinical effects remain unknown. 11 references.

003288 Stahl, S. M.; Meltzer, H. Y. Department of Psychiatry, University of Chicago Pritzker School of Medicine, Chicago, IL 60637 **Serotonin accumulation by skeletal muscle.** Experimental Neurology. 54(1):42-53, 1977.

The properties of serotonin accumulation by rat extensor digitorum longus muscles are characterized. No evidence was found for an active transport process because serotonin accumulation was unaffected by ouabain, metabolic inhibitors, or structural analogs. Serotonin transport was dependent on temperature and the external concentration of serotonin, was not saturable, and accumulated two to threefold higher than urea. These findings suggest that serotonin transport into skeletal muscle is mediated via passive diffusion followed by tissue binding. In vivo imipramine and chlorpheniramine, drugs which given with serotonin produce an acute myopathy, also inhibited its accumulation by rat extensor digitorium longus muscle. This supports the notion that the myopathy produced by serotonin plus membrane active drugs may be mediated by the action of serotonin upon the sarcolemma or upon the skeletal muscle vasculature in combination with the membrane action of imipramine and chlorpheniramine upon skeletal muscle membranes. 23 references. (Journal abstract)

003289 Stavinoha, W. B.; Hosoya, E.; Maruyama, Y.; Modak, A. T. Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX 78284 **Regional acetylcholine content in mouse brain after morphine tablet implantation.** Archives Internationles de Pharmacodynamie et de Therapie (Ghent). 225(1):58-63, 1977.

A study assessing the effects of implantation of a morphine tablet in mouse brains on regional acetylcholine levels in the brain is reported. Implantation of a 75 mg morphine tablet in mice caused a significant decrease in the body weight and hypothermia. After 3 days, the concentration of acetylcholine decreased in all brain regions with the exception of the cerebellum. A significant decrease in acetylcholine content was observed in the midbrain, corpus striatum and the cerebral cortex 3 days after implantation. It is postulated that the decrease in acetylcholine content is due to an increased release of acetylcholine as a result of development of tolerance to morphine. 22 references. (Author abstract)

003290 Stone, C. J.; Forney, R. B. Becton, Dickinson Research Center, Research Triangle Park, NC 27709 **The effects of phencyclidine on ethanol and sodium hexobarbital in mice.** Toxicology and Applied Pharmacology. 40(2):177-183, 1977.

The effects of phencyclidine (PCP) on ethanol and sodium hexobarbital in mice were investigated as well as disappearance of the drug from whole mouse and from selected tissues. Male albino mice were injected with saline alone or PCP plus sodium hexobarbital or ethanol, administered simultaneously or delayed 30 min. Loss of righting reflex (sleep time) was measured and a regression line was fitted to the data. In both cases, regression analysis indicated the existence of a clear dose response relationship. In the disappearance study, mice were injected with PCP and body tissues were homogenized at intervals ranging from 0 to 160 min. Disappearance studies indicated higher PCP concentrations in the liver and lung than in the brain. 10 references. (Author abstract modified)

003291 Stripling, Jeffrey S.; Ellinwood, Everett H., Jr. Behavioral Neuropharmacology Section, Department of Psychiatry, Box 3870, Duke University Medical Center, Durham, NC 27710 **Augmentation of the behavioral and electrophysiologic response to cocaine by chronic administration in the rat.** Experimental Neurology. 54(3):546-564, 1977.

The augmentation of the behavioral and electrophysiologic response to cocaine by chronic administration in the rat was studied. Male Sprague-Dawley rats were implanted with electrodes in the amygdala. After recovery, they were administered saline or one of two doses of cocaine for 13 days. The chronic administration of the high dose of cocaine resulted in augmentation of its behavioral and electrophysiologic effects. Subsequently the animals were given daily electrical stimulation of the amygdala to determine if the chronic cocaine administration had produced an effect in the

amygdala which would facilitate kindling. No significant facilitation was found, although this finding was considered inconclusive. A subsequent test injection of cocaine indicated that the augmentation of the electrophysiologic response to cocaine persisted for an average of 20 days or more. Persistence of the augmented behavioral effect was also found. Possible mechanisms underlying this augmentation were discussed. 35 references. (Author abstract modified)

003292 Suenaga, Noriko; Yamada, Katsushi; Fukuda, Takeo. Dept. of Pharmacology, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan **Correlation between central catecholamine level and post-decapitation convulsion in rats treated with 6-hydroxydopamine.** Brain Research (Amsterdam). 122(1):165-169, 1977.

The 6-hydroxydopamine (6-OHDA) induced alterations in catecholamine levels of various regions in the central nervous system and their relationships to changes in the incidence, latency, or duration of decapitation convulsion in rats were examined. Norepinephrine levels of the cortex, hypothalamus, and spinal cord were markedly decreased in the group given 6-OHDA without decapitation convulsion. In particular the depletion of norepinephrine in the spinal cord was directly correlated with prolongation of latency and shortening of duration of the convulsion. Cortical and hypothalamic norepinephrine levels also correlated with shortening of duration in the convulsion, but the values of the correlation coefficient were rather small, and there were no correlations between latency and catecholamine levels in these regions. The facts suggest that depletion of spinal norepinephrine might play the most important role in suppression of decapitation convulsion. However, the possibility of involvement of norepinephrine depletion in the cortex and hypothalamus in suppression of the convulsion cannot be ruled out. It is concluded that postdecapitation convulsion may be a release phenomenon from the tonic inhibition of inhibitory mechanism which is mediated by norepinephrine neurons, especially bulbo/spinal norepinephrine neurons. 13 references.

003293 Sun, G. Y.; Creech, D. M.; Corbin, D. R.; Sun, A. Y. Sinclair Comparative Medical Research Farm, University of Missouri, Columbia, MO 65001 **The effect of chronic ethanol administration on arachidonyl transfer to 1-acyl-glycerophosphorylcholine in rat brain synaptosomal fraction.** Research Communications in Chemical Pathology and Pharmacology. 16(4):753-756, 1977.

The effects of chronic ethanol administration on the enzymatic acylation of phosphoglycerides in the synaptosomal membranes are investigated. Enzymatic transfer of arachidonate to synaptosomal diacyl-glycerophosphorylcholine in a group of 14 rats administered 30% ethanol by intragastric intubation for 21 days was 24% higher than 5 controls. No apparent difference in enzymic activity was observed with respect to different periods of withdrawal (8 to 24 hrs). The acyl transferase activity in another group of rats which were given 15% ethanol as the sole drinking source for 13 months was 58% higher than controls. The increase in acyl transferase activity with respect to the two types of chronic ethanol administration may be due to an adaptive mechanism in brain to facilitate the increase in membrane transport activities which are known to occur under the influence of ethanol. 10 references. (Author abstract modified)

003294 Sylvia, A. L.; LaManna, J. C.; Rosenthal, M.; Jobsis, F. F. Department of Physiology and Pharmacology, Duke University Medical Center, Box 3709, Durham, NC 27710 **Metabolite studies of methamphetamine effects based upon mitochondrial respiratory state in rat brain.** Journal of Pharmacology and Experimental Therapeutics. 201(1):117-125, 1977.

Methamphetamine induced changes in metabolite levels were studied based upon a new approach to tissue sampling. In this procedure, the noninvasive, autoindicated redox state of intramitochondrial nicotinamide adenine dinucleotide hydrogen (NADH) was used to determine the point at which samples were taken rather than the time after drug injection. By this combination of in situ microfluorometry and tissue assay, a complex sequence of rapid changes in cerebral intermediary metabolism and associated mitochondrial redox shifts were observed. These changes were found to occur over a wide range of time course among animals after drug administration, and this temporal variation in response to the drug may be the factor for previously reported inconsistencies in metabolite patterns after methamphetaime. This finding emphasizes the potential difficulties that temporal variability produces in certain cerebral pharmacological responses and the value of the noninvasive, autoindicated redox keyed technique (NARK analysis) for metabolite sampling. 38 references. (Journal abstract modified)

003295 Szabadi, E.; Bradshaw, C. M; Bevan, P. Department of Psychiatry, University of Manchester, Stopford Building, Manchester M13 9PT, England **Excitatory and depressant neuronal responses to noradrenaline, 5-hydroxytryptamine and mescaline: the role of the baseline firing rate.** Brain Research (Amsterdam). 126(3):580-583, 1977.

The role of the baseline firing rate in the excitatory and depressant neuronal responses to noradrenaline (NA), 5-hydroxytryptamine (5HT), and mescaline is documented. Spontaneously active single neurons in the somatosensory cortices of halothane anesthetized cats were studied. Effects of NA were studied on 325 cells, and it was found that the proportion of excitations decreased and the proportion of depressions increased with increasing firing rates. Similar results were obtained from 252 cells with 5-HT and from 189 cells with mescaline. Results are consistent with the hypothesis that most cortical neurons contain both excitatory and depressant receptors for the monoamines and that the neuronal responses to the monoamines reflect a functional balance between the two types of receptor. Further, the relationship between excitatory and inhibitory receptors may be influenced by the baseline firing rate of the neuron: a low firing rate would favor the functional dominance of the excitatory receptors, whereas a high firing rate would shift the balance in favor of the inhibitory receptors. 13 references. (Author abstract modified)

003296 Szekely, Jozsef I.; Ronai, Andras Z.; Dunai-Kovacs, Zsuzsa; Miglecz, Erzsebet; Bajusz, Sandor; Graf, Laszlo. Research Institute for Pharmaceutical Chemistry, H-1325 Budapest, P.O. Box 82, Hungary **Cross tolerance between morphine and beta-endorphin in vivo.** Life Sciences. 20(7):1259-1264, 1977.

The cross-tolerance between morphine and the C-terminal fragment (61-91) of porcine beta-lipotropin (beta-endorphin) was tested by the tail flick method in rats. Repeated intracerebroventricular (ICV) or peripheral administration of morphine induced tolerance both to morphine and beta-endorphin. The tolerance induced by ICV administration of morphine was more pronounced than in the case of peripheral application. The results support the theory that at least in part similar sites and mechanisms are involved in the analgesic activity of morphine and the endorphins. 27 references. (Author abstract modified)

003297 Tagashira, Yukio; Matsuda, Masayuki; Welch, Kenneth M. A.; Chabi, Eva; Meyer, John S. Department of Neurology, Baylor College of Medicine, Houston, TX 77030 **Effects of cyclic AMP and dibutyryl cyclic AMP on cerebral hemodynamics and metabolism in the baboon.** Journal of Neurosurgery. 46(4):484-493, 1977.

To measure the influence of exogenous adenosine 3',5'-cyclic monophosphate (cyclic-AMP) on cerebral hemodynamics and energy metabolism in vivo, cyclic-AMP was infused into the carotid artery of baboons anesthesized with sodium pentobarbital, causing a biphasic increase in cerebral blood flow (CBF) and reduction in cerebrovasular resistance (CVR) associated in each phase with stimulation of cerebral metabolism evidenced by increased cerebral oxygen consumption (CMRO2) and cerebral glucose consumption (CMRG1). Intracarotid dibutyryl cyclic-AMP (0.5mg/kg) caused a monophasic increase in CBF and reduction of CVR but failed to alter cerebral metabolism. This may be due to its rapid removal from the circulation with ineffective passage across the blood-brain barrier since intracisternal infusion of dibutyryl cyclic-AMP caused sustained increase in CBF, CMRO2 and CMRG1 and reduction in CVR. Intracarotid AMP (0.4mg/kg) and adenosine (0.3mg/kg) caused an immediate and more marked increase in CBF and decrease in CVR unassociated with cerebral metabolic change making it unlikely that the observed effects of cyclic-AMP can be attributed to its breakdown products. Cyclic-AMP or its dibutyryl derivative may alter cerebral metabolism secondary to neuronal activation but increase in glucose/oxygen utilization ratio after intracarotid cyclic-AMP and intracisternal dibutyryl cyclic-AMP also suggests an influence on enzymatic regulation of glucose metabolism. 19 references. (Author abstract modified)

003298 Terenius, Lars. Department of Medical Pharmacology, University of Uppsala, Box 573, S-751 23 Uppsala, Sweden **Opioid peptides and opiates differ in receptor selectivity.** Psychoneuroendocrinology (Oxford). 2(1):53-58, 1977.

The receptor selectivity of opioid receptors in whole rat cerebrum was studied with tritium-labeled dihydromorphine, naltrexone, and Leu-enkephalin as radioindicators and various opioid peptides and opiates as competitors. Dihydromorphine showed high affinity binding to sites which were competitively blocked by various opiate agonists and atagonists (DHM sites). Naltrexone was bound to additional sites which also strongly bound other narcotic antagonists. The morphinomimetic enkephalins showed high selectivity for DHM sites while ACTH fragments and somatostatin showed less selectivity. Leu-enkephalin appeared to bind to separate sites (EKN sites) with similar affinity to that for DHM sites. Both dihydromorphine and naltrexone showed higher affinity for DHM sites than for EKN sites. It was suggested that the differences in receptor populations may relate to functional differences. 15 references. (Author abstract modified)

003299 Thadani, Pushpa V.; Lau, Christopher; Slotkin, Theodore A.; Schanberg, Saul M. Duke University Medical Center, P.O. Box 3709, Durham, NC 27710 **Effects of maternal ethanol ingestion on amine uptake into synaptosomes of fetal and neonatal rat brain.** Journal of Pharmacology and Experimental Therapeutics. 200(2):292-297, 1977.

The effects of maternal ethanol ingestion on amine uptake and synthesis in synaptosomes of fetal and neonatal rat brain were studied. Pregnant rats were kept on an ethanol containing (6.8% v/v) liquid diet either from the 13th or 18th day of gestation. In pups exposed to ethanol from the 13th day of gestation, synaptosomal uptake of 3H-tyramine and its conversion to 3H-octopamine were increased initially and exposure to ethanol from the 18th day of gestation produced increases in synaptosomal uptake and conversion for longer periods. These changes were not observed in adult rats administered ethanol. Brain tyrosin hydroxylase activity in the developing rats was unaltered by continuous exposure to ethanol. Withdrawal from ethanol either at 0, 3 or 5 days of age enhanced the tendency toward increased synaptosomal uptake and conversion, but the magnitude of change depended upon the time of exposure and the age at which withdrawal was initiated. These results suggest that maternal ethanol ingestion can affect synaptic function in the developing central noradrenergic system, with consequent alterations in neurotransmitter uptake and storage. 33 references. (Author abstract modified)

003300 Thomsen, Klaus. Psychopharmacology Research Unit, Aarhus University Institute of Psychiatry, DK-8240 Risskov, Denmark **The renal handling of lithium: relation between lithium clearance, sodium clearance and urine flow in rats with diabetes insipidus.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(4):491-496, 1977.

The relation between the lithium clearance and urine flow in rats which had hereditary lack of vasopressin production and which had been given a test dose of lithium were studied to determine the renal handling of lithium. The two variables were altered by varying the sodium intake. Rats with a low, medium and high sodium intake had a mean lithium clearance of 0.04, 0.22, and 0.40 ml/min/100g bodyweight, respectively. When the sodium intake was increased from a medium to a high level, the lithium clearance and the urine flow rose in proportion to each other. When the sodium intake was decreased from a medium to a low level, the lithium clearance fell relatively more than the urine flow so that the proportion between the two was changed. The experiments show that when vasopressin induced alterations of the urine flow are excluded and when the sodium intake is not extremely low, proportionality may occur between the lithium clearance and the urine flow. This suggests that the lithium clearance varies in proportion to and is determined by the delivery of sodium from the proximal tubules. 11 references. (Author abstract modified)

003301 Tofanetti, O.; Albiero, L.; Galatulas, I.; Genovese, E. Laboratory of Pharmacology, Boehringer Biochemia, Milan, Italy **Enhancement of propoxyphene-induced analgesia by doxepin.** Psychopharmacology (Berlin). 51(2):213-215, 1977.

The activity of the centrally acting analgesic, propoxyphene, alone and in combination with the tricyclic antidepressant, doxepin, was studied in mice. Doxepin, in doses lacking any analgesic effects alone, significantly potentiated the analgesic activity of propoxyphene when administered orally or intraperitoneally. The acute toxicity of propoxyphene was not significantly altered by doxepin. 14 references. (Author abstract modified)

003302 Tokunaga, Yukiko; Muraki, Takamura; Hosoya, Eikichi. Dept. of Pharmacology, School of Medicine, Keio University, Shinjuku-ku, Tokyo 160, Japan **Effects of repeated morphine administration on copulation and on the hypothalamic-pituitary-gonadal axis of male rats.** Japanese Journal of Pharmacology (Kyoto). 27(1):65-70, 1977.

Adult male rats were administered morphine twice a day for 45 days and the effects of morphine on the copulation rate, the weight of various organs, and on the hypothalamic/pituitary/gonadal axis were examined. Morphine administered rats showed a loss of weight, hypertrophy of the

adrenals, decreased weight of accessory sex organs, low sperm count, and decreased copulation rate. The contents of the luteinizing hormone releasing hormone in the hypothalamus and the luteinizing hormone in the pituitary remained unchanged. Serum luteinizing hormone and testosterone levels decreased, but serum follicle stimulating hormone levels increased. These results suggest that morphine inhibits the hypothalamic/pituitary/gonadal axis and causes a diminution in the number of fertilizations of the partner females. 10 references. (Author abstract)

003303 Tricklebank, M. D.; Pickard, F. J.; Dobbing, J. Dept. of Child Health, Medical School, University of Manchester, Oxford Road, Manchester M13 9PT, England **Tryptophan and 5-hydroxytryptamine metabolism in the immature rat brain during recovery from asphyxia.** Journal of Neurochemistry (Oxford). 28(3):641-644, 1977.

Cerebral 5-hydroxytryptamine (5-HT) accumulation and turnover was studied in neonatal rats (age 5 days) by determining 5-hydroxyindoleacetic acid concentration with and without inhibition of monoamine oxidase (MAO) by tranylcypromine to investigate alterations of brain metabolism during recovery from asphyxia. Marked increases in turnover were found to persist for up to 3 h after resuscitation and was accompanied by increases in brain tryptophan, plasma total tryptophan and the fraction of the plasma total tryptophan that was not bound to albumin. None of these parameters were different from those in control animals 24 h after resuscitation. Brain and plasma tyrosine levels remained unaltered by the treatment at all times investigated. It is suggested that 5-HT may in some way modulate severity of neurological damage following asphyxial/ischemic insult to the adult or immature nervous system during human development. 21 references. (Author abstract modified)

003304 Trimble, Mike; Anlezark, Gill; Meldrum, Brian. Department of Neurology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, England **Seizure activity in photosensitive baboons following antidepressant drugs and the role of serotoninergic mechanisms.** Psychopharmacology (Berlin). 51(2):159-164, 1977.

The effects of imipramine, chlorimipramine, maprotiline, and nomifensine on seizure activity were studied in baboons with photosensitive epilepsy. Imipramine, chlorimipramine and maprotiline lowered seizure threshold to a comparable extent. Nomifensine did not enhance myoclonic responses to photic stimulation. Generalized seizures occurred after imipramine or chlorimipramine. Administration of 5-hydroxytryptophan prior to imipramine or chlorimipramine completely blocked the augmentation of photically induced epileptic responses. It is concluded that enhancement of serotoninergic activity following blockade of serotonin reuptake within the brain is unlikely to be responsible for enhanced myoclonic responses and epileptogenic seizures seen after tricyclic antidepressants. 39 references. (Author abstract modified)

003305 Tuomisto, Jouko. Department of Pharmacology, University of Helsinki, SF-00170 Helsinki, Finland **Nomifensine and its derivatives as possible tools for studying amine uptake.** European Journal of Pharmacology (Amsterdam). 42(2):101-106, 1977.

The effects of nomifensine (NOM) and three of its derivatives on the uptake of noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) in rat brain synaptosomes were studied. NOM was a potent inhibitor of NA and DA uptake, but a relatively weak inhibitor of 5-HT uptake. According to kinetic studies of DA uptake, the inhibition was competitive. The percentage inhibition did not increase with time, suggesting that inhibition of membrane uptake rather than inhibition of storage was the mechanism of action. The addition of a 4-hydroxy group to the phenyl ring of NOM, (8-amino-2-methyl-4(4-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline), slightly decreased the potency, and addition of hydroxy and methoxy groups to the positions 3 and 4 in the phenyl ring, (8-amino-2-methyl-4(3-methoxy-4-hydroxyphenyl) and 8-amino-2-methyl-4-(3-hydroxy-4-methoxyphenyl)-1,2,3,4-tetrahydroisoqu noline), decreased the potency. The structure of NOM was compared to that of chlorimipramine (CP). It was suggested that the differences in selectivity as to DA and 5-HT uptake mechanisms might be due to two conformational differences; one of the phenyl rings is freely rotating in NOM but not in CP, and the tertiary amine group is in a flexible side chain in CP but rigidly tied in NOM. 15 references.

003306 Turkanis, Stuart A.; Chiu, Pauline; Borys, Henry K.; Karler, Ralph. Department of Pharmacology, University of Utah College of Medicine, Salt Lake City, UT 84132 **Influence of delta9-tetrahydrocannabinol and cannabidiol on photically evoked after-discharge potentials.** Psychopharmacology (Berlin). 52(2):207-212, 1977.

Delta9-tetrahydrocannabinol (THC), cannabidiol (CB) and several reference drugs were compared relative to their effects in an anticonvulsant test system, the afterdischarge potentials of photically evoked response in rats. The potentials were recorded electrophysiologically from electrodes permanently mounted over the visual cortices of conscious rats. In anticonvulsant doses, trimethadione and ethosuximide produced an extensive depression of afterdischarge activity (ADA), whereas diphenylhydantoin and CB exerted no such effect. In contrast, anticonvulsant doses of THC and subconvulsant doses of pentylenetetrazol markedly increased ADA, which may represent a manifestation of their central nervous system excitation properties. The results indicate the anticonvulsant characteristics of CB resemble those of diphenylhydantoin rather than those of trimethadione and that the central excitatory properties of THC distinguish it from CB. The results suggest that the cannabinoids will be effective against grand-mal but not absence seizures. 38 references. (Author abstract modified)

003307 Tzeng, Sinfu; Ho, Ing K. Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS 39216 **Effects of acute and continuous pentobarbital administration on the gamma-aminobutyric acid system.** Biochemical Pharmacology (Oxford). 26(8):699-704, 1977.

Effects of acute anesthetic doses and chronic administration of pentobarbital on gamma-aminobutyric acid (GABA) and glutamic acid levels were investigated in mouse brain tissue. Acute administration of pentobarbital caused an increase in the brain level of GABA which was associated with pentobarbital induced narcosis. This was further substantiated by the finding that pentobarbital induced sleeping time was prolonged when brain GABA level was elevated by the administration of either aminooxyacetic acid (AOAA) or glutamate. In addition, the activity of L-glutamate-1-carboxylase (GAD) measured during pentobarbital induced narcosis was higher than that of the control group. Chronic administration of pentobarbital resulted in a decrease of both GABA and glutamate levels, and a concomitant decrease in the activity of GAD, confirmed by the finding that the rate of brain GABA accumulation induced by AOAA administration in tolerant mice was slower than that of the nontolerant animals. Brain GABA remained at

significantly lower levels after an abrupt withdrawal from pentobarbital; however, brain glutamate levels showed no significant difference as compared to the control group. It appears that the GABA system in the CNS may be involved in barbiturate narcosis and further linked with the development of tolerance to barbiturate. 28 references. (Author abstract modified)

003308 Ungar, Frieda; Callaghan, Owen H. Department of Biochemistry, Chicago Medical School, Chicago, IL 60612 **Studies on membrane receptor sites for serotonin in the brain.** Research Communications in Chemical Pathology and Pharmacology. 16(2):205-224, 1977.

A study was undertaken using mouse, rat and calf brain tissues to characterize the serotonergic receptors in the central nervous system. Morphine and chlorpromazine decreased the borohydride stabilizable binding of radiolabeled 5-hydroxytryptamine (5-HT) to rat brain slices, but 5,6-dihydroxytryptamine produced a greater decrease. The subsynaptosomal localization of the binding of morphine in bovine midbrain preparations was compared to that of 5-HT and found to be considerably higher. Evaluation of these and other results points to a 5-HT membrane receptor macromolecule which is a proteolipid possessing activated receptor carbonyl residues. 13 references.

003309 Ungar, G.; Ungar, A. L.; Malin, D. H.; Sarantakis, D. Department of Biochemistry, University of Tennessee, Center for the Health Sciences, Memphis, TN 38163 **Brain peptides with opiate antagonist action: their possible role in tolerance and dependence.** Psychoneuroendocrinology (Oxford). 2(1):1-10, 1977.

The possible role in tolerance and dependence of rat brain peptides with opiate antagonist action was studied. Extracts of brain taken from rats injected with increasing doses of morphine acted like antagonists on an electrically stimulated mouse vas deferens preparation in vitro and on morphine analgesia in mice in vivo. After electrophoretic fractionation, the antagonist properties were found among the basic peptides. One of these, Arg-Tyr-Gly-Gly-Phe-Met, was synthesized and reproduced the analgesia inhibiting effect of the brain extract. However, it did not show antagonist properties on mouse vas deferens, but acted like enkephalin. Quantitative estimation of the agonist and atagonist concentration in the brain of morphine injected rats showed increases in both types of peptides during the first 12 days of treatment followed by a particularly marked fall of the agonists, far below the normal level. The endogenous antagonist and the synthetic peptide precipitated opiate withdrawal symptoms in preliminary experiments, suggesting they may be involved in the mechanism of dependence. The results suggest the possibility that a shift in the balance of endogenous agonists and antagonists may contribute to the development of tolerance and dependence. 28 references. (Author abstract modified)

003310 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Neuroleptics and CA-ergic transmission in the brain: animal experiments.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 189-197).

Animals studies of the effects of neuroleptics on catecholaminergic transmission in the brain are reviewed. Neuroleptics of the phenothiazine, butyrophenone, thioxanthine, and diphenylbutylpiperidine types increase the intracerebral turnover of the catecholamines (CA) dopamine (DA), and noradrenalin (NA). This effect is probably secondary to postsynaptic DA and NA receptor block and inhibition of DA release into the synaptic cleft after stimulation of the axon. The extent to which the various neuroleptics specifically influence DA and NA receptors differs widely. This biochemical differentiation does not coincide with classification on the basis of chemical structure. The neuroleptics reserpine (a Rauwolfia alkaloid) and oxypertine (an indole derivative) do not block DA receptors. These drugs inhibit the uptake of DA into the storage vesicles, causing an increased degree of degradation by monoamine oxidase and reducing the amount of transmitter substance available for release. It has been demonstrated that all of the known neuroleptics inhibit transmission in catecholaminergic neuronal systems.

003311 Van Ree, Jan M.; De Wied, David. Rudolph Magnus Institute for Pharmacology, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands **Effect of neurohypophyseal hormones on morphine dependence.** Psychoneuroendocrinology (Oxford). 2(1):35-41, 1977.

The effect of neurohypophyseal hormones on morphine dependence was studied in rats. The degree of physical dependence was measured by the loss of body weight following an injection of naloxone in rats chronically treated with morphine. Oxytocin was approximately 5 times more potent than (desglycinamide-9-arginine-8)-vasopressin (DG-AVP) in naloxone induced body weight loss. The covalent ring of oxytocin (tocinamide) was ineffective, but the C-terminal tripeptide of oxytocin (PLG) appeared to be more potent than oxytocin. The response latency of animals to heat was measured on a hot plate before and after treatment with morphine and naloxone. The response latency was decreased in animals pretreated with oxytocin and PLG approximately 5 times more than in rats pretreated with DG-AVP, the cyclic peptide AVT, or Pro-Arg-Gly-NH2 (PAG). The results with these and other peptides suggest that the essential elements of vasopressin and oxytocin required for facilitating morphine tolerance and physical dependence are located in the C terminal part of the hormones. 24 references.

003312 Van Zwieten, P. A. Dept. of Pharmacy, Univ. of Amsterdam, Plantage Muidergracht 24, Amsterdam-C, The Netherlands **The interaction between clonidine and various neuroleptic agents and some benzodiazepine tranquillizers.** Journal of Pharmacy and Pharmacology (London). 29(4):229-234, 1977.

The influence of various phenothiazine/neuroleptics and some benzodiazipines on the hypotensive effect of clonidine was studied in anesthetized cats. The central hypotensive action of clonidine was antagonized by several phenothiazine neuroleptics (chlorpromazine, promazine, promethazine, thiethylperazine, thioridazine), by chlorprothixene and to a limited extent by haloperidol administered via the same route. Pimozide and some benzodiazepines (chlordiazepoxide, diazepam and flurazepam) hardly influenced the central hypotensive response to clonidine. The antagonism between clonidine and the psychotropic drugs is probably associated with central alpha-adrenoceptors, clonidine being the agonist and the neuroleptic agents the antagonists at these receptors. Virtually the same type of antagonism was observed in conscious, spontaneously hypertensive rats where both clonidine and the neuroleptic drugs were injected intravenously. The phenothiazines and also piperoxane effectively diminished the centrally induced hypotensive response to clonidine, whereas the initial pressor effect to clonidine was not reduced. 19 references. (Author abstract)

003313 Velasco, M.; Velasco, F.; Cepeda, C.; de Anda, A. M. Division of Neurophysiology, Scientific Research Department,

National Medical Center, IMSS, P.O. Box 73-032, Mexico, D.F., Mexico **Effect of diazepam on pyramidal tract and electromyographic multiple unit activities of cats with chronic epileptogenic foci.** Neuropharmacology. 16(4):299-301, 1977.

The effect of diazepam on pyramidal tract (PT) and electromyographic (EMG) multiple unit activities (MUA) was quanitatively determined on cats with alumina cream focal motor epilepsy. Concomitant changes in electroencephalogram (EEG) and EMG convulsivity and vigilance level of the cats were also measured. Diazepam produced 2 consecutive responses, an initial "arousal like" response consisting of behavioral alertness and motor hyperactivity, with electrophysiological signs of reticular activation, decreased number of epileptic EEG spikes, and no changes in EMG convulsions. It was associated with a significant increase in tonic PT and EMG MUA with no significant changes in phasis PT MUA. A second "sleep like" response consisted of behavioral lethargy and hypotonia, with electrophysiological signs of reticular deactivation, increased number of epileptic EEG spikes, and amplitude reduction of EMG convulsions. It was associated with a significant decrease in tonic PT and EMG and phasic PT MUA. The results suggest that diazepam blocks clinical convulsions by deactivation of the cortical and spinal mechanisms mediating epileptic impulses from the cerebral cortex to muscles. 11 references. (Author abstract modified)

003314 Vigouret, J. M.; Loew, D. M.; Jaton, A. L. Biological and Medical Research Division, Sandoz Ltd., CH-4002 Basel, Switzerland **Effects of bromocriptine on alpha- and gamma-rigidity in rats in comparison to apomorphine and d-amphetamine.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R54, 1977.

A study of the effects of bromocriptine on reserpine induced alpha and gamma rigidity in rats in comparison to apomorphine and d-amphetamine is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. Bromocriptine reduced or abolished alpha rigidity induced by reserpine after intercollicular decerebration in rats but had no effect on gamma rigidity. Apomorphine and dextro amphetamine also inhibited alpha rigidity in a dose dependent manner but had no effect on gamma rigidity. It is suggested that the inhibition of alpha rigidity after bromocriptine treatment, which is assumed to be representative of the rigidity observed in Parkinson patients, is mediated via stimulation of dopaminergic substrates and that this action could explain the therapeutic effect on rigidity in Parkinson patients. 5 references. (Author abstract modified)

003315 Vogel, W. H.; Trendelenburg, U. Thomas Jefferson University, Philadelphia, PA 19107 **Alpha-and-beta-activity of O-methylated derivatives of norepinephrine and epinephrine.** Experientia (Basel). 33(2):260-261, 1977.

Metanephrine, isometanephrine, normetanephrine, and isonormetanephrine were tested for alpha and beta activity on various tissues obtained from rats, guinea pigs, and cats. It was found that O-methylation of the hydroxyl groups of norepinephrin or epinephrine in either the 3 or 4 position markedly reduces or abolishes alpha or beta activity with the exception of the nictitating membrane of the cat. This receptor seems to show a tissue rather than a species difference. 8 references. (Author abstract modified)

003316 Volicer, L.; Hurter, B. P. Department of Pharmacology, Boston University School of Medicine, 80 East Concord St., Boston, MA 02118 **Effects of acute and chronic ethanol administration and withdrawal on adenosine 3′:5′-monophosphate and guanosine 3′:5′-monophosphate levels in the rat brain.** Journal of Pharmacology and Experimental Therapeutics. 200(2):298-305, 1977.

The effects of acute and chronic ethanol administration and withdrawal on adenosine 3′,5′-monophosphate (cAMP) and guanosine 3′,5′-monophosphate (cGMP) levels in rat brain were studied. The rats were sacrificed by microwave irradiation, the brains divided into 4 areas, and the cyclic nucleotides were measured by radioimmunoassays. Administration of a single dose of ethanol per os produced a dose dependent decrease of cAMP in cerebral cortex, cerebellum, pons, and medulla oblongata while cGMP was also decreased in the subcortex. Dependence on ethanol was induced by 3 daily administrations of ethanol for 7 days. The last dose did not produce any decrease of cAMP levels while the decrease of cGMP was still present. Animals withdrawn 12 or 24 hrs from ethanol after 7 days of chronic administration of ethanol showed higher incidence of tremor, startle to noise, audiogenic seizures, and convulsions on handling than control rats. During ethanol withdrawal cAMP levels increased in cerebral cortex, pons, and medulla oblongata and did not change in cerebellum. Changes of cAMP in subcortex were more complex. During withdrawal cGMP levels increased in cerebellum, pons, and medulla oblongata and did not change in cerebral cortex and subcortex. The results indicate that changes of cyclic nucleotides might participate in the mechanism of ethanol dependence and withdrawal. 55 references.

003317 Wagner, J. G.; Weidler, D. J.; Hallmark, M. R.; Black, K. L.; Domino, E. F. University of Michigan, College of Pharmacy, Ann Arbor, MI 48109 **Pharmacokinetics of pentobarbital in the cat and comparisons with the rabbit and man.** Research Communications in Chemical Pathology and Pharmacology. 16(2):375-384, 1977.

The pharmacokinetics of pentobarbital were investigated in the cat by measurement of pentobarbital plasma concentrations as a function of time after intravenous administration of doses ranging from 12.5mg/kg to 50mg/kg. Pharmacokinetic linearity was evidenced by the calculated mean plasma clearance and by a linear relationship between total area under the curve and mg/kg dose in one cat given three different doses of the drug. However, the apparent elimination half-life had a large coefficient of variation. In one cat, the half-life was the same after administration of 25mg/kg and 50mg/kg, but after 12.5mg/kg the half-life was considerably lower. There was also evidence of kinetic nonlinearity in the initial falloff portions of some of the curves. Results were compared with literature data for rabbits and man. Plasma clearances are greatest in the rabbit, substantially less in the cat, and least in man. In the rabbit and cat, there were no significant correlations between calculated pharmcokinetic parameters and mg/kg doses using data from all animals studied; this also suggests kinetic linearity. 9 references. (Author abstract modified)

003318 Wajda, Isabel J.; Manigault, Issac; Hudick, James P. Neurochemistry and Drug Addiction, Rockland Research Institute, Ward's Island, New York, NY 10035 **Dopamine levels in the striatum and the effect of alcohol and reserpine.** Biochemical Pharmacology (Oxford). 26(7):653-655, 1977.

In order to examine the effects of acute and chronic alcohol administration on neural transmission processes and dopamine (DA) levels in the corpus striatum of rats, the choline acetyltransferase and tyrosine hydroxylase (TH) activities were assayed and DA levels determined in rats subjected to prolonged ethanol administration or rats injected intraperitoneally with

ethanol. Behavioral concomitants of acute and chronic ethanol administration are described. It was found that acute administration of ethanol increased steady state levels of DA within 1 hour of administration and that levels of DA returned to normal within 4 hours of a dose which caused intoxication but not loss of the righting reflex. Higher levels of DA were found in the striatum of rats treated chronically with alcohol and remained high after 48 hours of abstinence. No changes in TH or choline acetyltransferase activities were found in any of the test animals. To test the possible influence of ethanol on the adrenergic storage sites, DA levels were determined for reserpine alone and reserpine plus alcohol; however, no significant differences between DA levels in the 2 conditions were found. 19 references.

003319 Walker, J. Michael; Berntson, Gary G.; Sandman, Curt A.; Coy, David H.; Schally, Andrew V.; Kastin, Abba J. Department of Psychology, Ohio State University, Columbus, OH 43210 **An analog of enkephalin having prolonged opiate-like effects in vivo.** Science. 196(4285):85-87, 1977.

The possibility that endogenous enkephalins may act to modulate pain systems is investigated using the enkephalin analog (D-ala 2)-metenkephalin. Intraventricular administration of the (D-ala 2) analog induces profound and long-lasting analgesia, as well as other opiate-like behavioral effects in the rat. This analgesia was highly dose dependent, of much greater magnitude, and about 30 times longer lasting than that produced by the naturally occurring peptide, methionine enkephalin. The behavioral effects of the analog could be completely reversed by the opiate antagonist, naloxone, suggesting that these effects were mediated by opiate receptors. Systemic administration of naloxone alone resulted in a significant increase in pain sensitivity. These findings support the view that endogenous opiate systems may play an important role in modulating pain sensitivity. 25 references. (Author abstract modified)

003320 Wang, Rex Y.; Aghajanian, George K. Departments of Psychiatry and Pharmacology, Yale University School of Medicine, New Haven, CT 06508 **Inhibition of neurons in the amygdala by dorsal raphe stimulation: mediation through a direct serotonergic pathway.** Brain Research (Amsterdam). 120(1):85-102, 1977.

The effects of iontophoretic application of 5-hydroxytryptamine (5-HT) on amygdaloid neuronal firing rates were studied in the rat in conjunction with the responses of the same neuron to stimulation of the dorsal raphe nucleus (DRN). Both 5-HT and electrical stimulation of the DRN markedly inhibited spontaneous single unit activities of the same amygdaloid cells. The latency of DRN induced inhibition was relatively short and was compatible with the conduction velocities of unmyelinated 5-HT fibers. Destruction of 5-HT projections by 5,7-dihydroxytryptamine or pharmacological depletion of 5-HT by parachlorophenylalanine (PCPA) prevented the inhibitory responses to DRN stimulation in the great majority of cells studied. In PCPA pretreated animals, injection of 5-hydroxytryptophan reversed the PCPA effect and restored the responses of amygdaloid cells to DRN stimulation. The inhibitory effects of 5-HT in the amygdala were not blocked by administration of several presumptive 5-HT antagonists. However, intravenously administered LSD blocked the inhibitory responses produced by submaximal DRN stimulation. It is suggested the DRN has a marked inhibitory influence upon neurons in the amygdala and that this inhibitory effect is mediated by a direct DRN/amygdala serotonergic pathway. The implications of the results for the possible functions of 5-HT in the amygdala are discussed. 49 references. (Author abstract modified)

003321 Wasterlain, Claude G.; Fando, Juan L.; Lieber, Charles S. no address **Chronic alcohol ingestion inhibits rat brain protein synthesis.** Neurology. 27(4):385, 1977.

AT a metting of the american Academy of Neurology in Atlanta, GA in April, 1977, the effects of chronic alcohol ingestion on rat brain protein synthesis was studied by measuring the incorporation of 14C-valine and 3H-leucine in brain and other organs of littermates fed either a diet containing 36 percent of calories as ethanol or a diet in which carbohydrates were isocalorically substituted for ethanol. Ethanol inhibited protein synthesis in forebrain, cerebellum, and brainstem. No difference was observed in specific activity of precursor pools. Leucine incorporation into protein was inhibited in vitro in a cell free system from brains of alcohol drinking rats. A similar load of alcohol acutely given to rats did not inhibit protein synthesis in the brain. Liver, lung, kidney, and spleen showed no effect of alcohol ingestion; inhibition of heart and skeletal muscle protein synthesis in alcohol fed rats approached significance. The results suggest that in rats chronic alcohol ingestion inhibits brain protein synthesis in the absence of of malnutrition.

003322 Waterfield, Angela A.; Smokcum, Roger W. J.; Hughes, John; Kosterlitz, Hans W.; Henderson, Graeme. Unit for Research on Addictive Drugs, University of Aberdeen, Marischal College, Aberdeen AB9 1AS, Scotland **In vitro pharmacology of the opioid peptides, enkephalins and endorphins.** European Journal of Pharmacology (Amsterdam). 43(2):107-116, 1977.

An in vitro study of the pharmacology of the two opioid peptides, enkephalins and endorphins, using guinea pig ileum and brain homogenate, and mouse vas deferens, is presented. It was found that methionine enkephalin, normorphine, and morphine are equipotent in depressing electrically evoked contractions in the guinea pig ileum, while leucine enkephalin has about 25% of the activity. The mouse vas deferens is more sensitive to the enkephalins which are 30 to 60 times more potent than morphine. Fragments of beta-lipotropin61-91 (beta-endorphin) having sequences up to lipotropin 76 are more potent in the mouse vas deferens than in the guinea pig ileum but beta-endorphin is about equipotent in the two preparations. None of the peptides has antagonist activity. Methionine enkephalin and normorphine are equipotent in inhibiting (3H)-naloxone binding by homogenate ileum, naloxone antagonises normorphine and the enkephalins equally well whereas in the mouse vas deferens about ten times more naloxone is required for the enkephalins than for normorphine. Methionine enkephalin depresses output of acetylcholine in the guinea pig ileum and of noradrenaline in the mouse vas deferens. 35 references. (Author abstract)

003323 Westerink, Ben H. C.; Lejeune, Bernard; Korf, Jakob; Van Praag, Herman M. Department of Clinical Chemistry, Antonius Deusinglaan 2, State University, Groningen, The Netherlands **On the significance of regional dopamine metabolism in the rat brain for the classification of centrally acting drugs.** European Journal of Pharmacology (Amsterdam). 42(2):179-190, 1977.

The significance of regional dopamine metabolism in the rat brain for the classification of centrally acting drugs was studied by measuring 3,4-dihydroxyphenylacetic acid (DPA) and homovanillic acid (HVA) in the corpus striatum, nucleus accumbens and tuberculum olfactorium. A rise of DPA and

HAVA in the three brain regions was induced by the following: amitriptyline, chlorimipramine, doxepine, nortriptyline, chloral hydrate, pentobarbital, ether, halothane, dipropylacetate, ethosuximide and metoclopramide. No change was observed after carbamazepine, diazepam or propranolol treatment. Combined treatment with a maximally effective dose of haloperidol and morphine, oxotremorine or probenecid produced an additional rise of DPA and HVA levels, while no additional rise was seen with chloral hydrate, chlorimipramine, ether, halothane, metoclopramide, or sulpiride. The potency of drugs to increase dopamine metabolism in corpus striatum relative to mesolimbic structures was estimated. Atypical neuroleptics: clozapine, sulpiride, and thioridazine could be differentiated from classical neuroleptics such as chlorpromazine, fluphenazine and thioproperazine by their ability to produce a relatively large increase of metabolite levels in the mesolimbic regions. The heterogeneous group of 14 nonneuroleptics produced regional changes which were very similar to those of the atypical neuroleptics. Dopamine metabolism in mesolimbic regions, in contrast to striatal tissue, seems to respond more to atypical neuroleptics and nonneuroleptics than to typical neuroleptics. 50 references. (Author abstract modified)

003324 Whishaw, Ian Q.; Schallert, Timothy. Department of Psychology, University of Lethbridge, Lethbridge, Alberta, Canada **Hippocampal RSA (theta), apnea, bradycardia and effects of atropine during underwater swimming in the rat.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(3):389-396, 1977.

Hippocampal rhythmical slow activity (RSA or theta rhythm), apnea, bradycardia, and the effects of atropine were studied during underwater swimming in the rat. Simple techniques for obtaining electroencephalograms and electrocardiograms during surface and underwater swimming were described. RSA was present with slightly reduced frequency during the apnea, bradycardia, and vibrissae arrest associated with underwater swimming. Atropine sulfate blocked bradycardia but did not affect RSA. No causal relation was found between RSA and respiration, heartrate, or vibrissae movement. The results support the view that RSA is related to the neural control of voluntary movement. It was suggested that the slight reduction in RSA frequency during underwater swimming may be part of an oxygen conservation process. 27 references.

003325 Wilk, Sherwin; Stanley, Michael. Department of Pharmacology, Mount Sinai School of Medicine, Fifth Avenue and 100 Street, New York, NY 10029 **Perlapine and dopamine metabolism: prediction of antipsychotic efficacy.** European Journal of Pharmacology (Amsterdam). 41(1):65-72, 1977.

A model for the prediction of antipsychotic efficacy based on the dose dependent increase in levels of 3, 4-dihydroxyphenylacetic acid (DOPAC) in the striatum and tuberculum olfactorium of the rat is presented. The effect of perlapine, a sedative agent reported to lack antipsychotic efficacy, was compared to haloperidol, chlorpromazine and clozapine. All four drugs produced a dose dependent increase in DOPAC in both structures. The potency of perlapine was similar to that of chlorpromazine. Dopamine content was not altered by perlapine. The time/action curves for perlapine and clozapine were virtually identical in both brain structures. All four drugs also elevated homovanillic acid to a similar extent. It is suggested that perlapine should be reevaluated clinically and it is predicted that such trials will reveal that perlapine does possess antipsychotic efficacy. 34 references. (Author abstract modified)

003326 Wilk, Sherwin; Stanley, Michael. Department of Pharmacology, Mount Sinai School of Medicine, City University of New York, New York, NY 10029 **Dopamine and schizophrenia.** Lancet (London). No. 8002:94-95, 1977.

In a letter to the editor, arguments are presented in contrast to the hypothesis of Dr. Crow and his colleagues that the therapeutic effect of neuroleptics is dependent on their action in mesolimbic structures based on the increase of homovanillic acid (HVA) in the striatum and nucleus accumbens of the rat using a single dose of three neuroleptics at a single time point. It is suggested that an apparent differential sensitivity may be due to differences in time to peak response in the two structures. Furthermore, it is felt complete dose response and time action curves are necessary before any valid conclusions on regional selectivity are drawn. Regional selectivity, therefore, does not explain the pharmacological profile of drugs such as clozapine or thioridazine. 10 references.

003327 Wolfarth, S.; Dulska, E.; Harasiewicz, A. Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, 12 Smetna Street, Polen, Poland **The participation of the nigrothalamic pathway in the nigral control of the caudate nucleus.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R55, 1977.

A study of the participation of the nigrothalamic pathway in the nigral control of the caudate nucleus is reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft held in Mainz, Germany, in March, 1977. Unilateral administration of carbachol (CCh) directly into the lateral part of the substantia nigra (SN) of rabbits augmented the portion of alert pattern in the electroencephalogram (EEG) as well as evoked EEG epileptoidal discharges. CCh induced sniffing, ipsilateral and contralateral turning behavior, and abnormal forepaw movements which may have indicated local convulsion. Ipsilateral turnings appeared concomitantly with EEG discharges in the lateral SN, while contralateral turnings appeared together with discharges in the ventrolateral thalamus. After CCh injection into the medial part of SN, EEG epileptoidal discharges appeared primarily in SN. CCh injection in the medial SN produced no contralateral turning. After lesioning of the nigroneostriatal pathway, CCh injected into the lateral SN induced early and long-lasting discharges in SN, while in the caudate nucleus and cerebral cortex, these events appeared much later. In addition, the contralateral turning was weaker while the ipsilateral turning was stronger. All CCh induced effects were prevented by prior intranigral administration of atropine or gallamine. It is suggested that: 1) both the nigrothalamic pathway and the nigroneostriatal pathway control striatal neuronal activity; 2) the nigrothalamic pathway mother cells are grouped mostly in the lateral SN; and 3) these cells are cholinoceptive. (Author abstract modified)

003328 Wong, David T.; Horng, Jong S. Lilly Research Laboratories, Indianapolis, IN 46206 **Affinities of opiate agonists and antagonists for the enkephalin receptors of rat brain.** Research Communications in Chemical Pathology and Pharmacology. 16(4):749-752, 1977.

The affinities of opiate agonists and antagonists for the receptor of methionine enkephalin in rat brain homogenate are studied in light of the possibility that enkephalin or a related peptide is the endogenous ligand of the receptors which bind and mediate the pharmacological effects of opiates. The binding of 3H-enkephalin (methionine-enkephalin) to membranes of rat brain is inhibited by enkephalin and levorphanol with IC50 values of 5 and 1.6nM, respectively. Dextrorphan, the optical

isomer of levorphanol, is over 6,000 times less effective. Opiate agonists, morphine, dihydromorphine and levomethadone and opiate antagonists, naltrexone and naloxone are less effective inhibitors of 3H-enkephalin than in 3H-dihydromorphine and 3H-naloxone binding. However, opiates without the oxygen bridge as in the structure of morphine, such as levorphanol and the benzomorphans show affinities for the receptors of 3H-enkephalin equal or greater than their affinities for the receptors of 3H-opiates. 11 references. (Author abstract modified)

003329 Wright, Jeremy; Cho, Arthur K.; Gal, Joseph. Department of Pharmacology, School of Medicine, University of California, Los Angeles, CA 90024 **The role of N-hydroxyamphetamine in the metabolic deamination of amphetamine.** Life Sciences (Oxford). 20(3):467-474, 1977.

The formation of 1-phenyl-2-propanol from amphetamine and N-hydroxyamphetamine was measured in rabbit liver homogenates to examine the role of N-hydroxyamphetamine in the deamination of amphetamine. The alcohol was measured because phenylacetone is rapidly and completely reduced in the incubation mixture. In separate incubations, alcohol formation was more rapid from amphetamine than from N-hydroxyamphetamine. When deuterium labeled amphetamine was incubated in the presence of N-hydroxyamphetamine, the 2H/1H ratio for alcohol decreased while that for hydroxylamine increased with time. These experiments suggest that although the alcohol or ketone can form from N-hydroxyamphetamine, it is not an obligatory intermediate from amphetamine. 20 references. (Author abstract modified)

003330 Wurtman, Richard J.; Watkins, Carol J. Lab. of Neuroendocrine Regulation, Dept. of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, MA 02139 **Suppression of noradrenaline synthesis in sympathetic nerves by carbidopa, an inhibitor of peripheral dopa decarboxylase.** Nature (London). No. 5589:79, 1977.

To test the effect of carbidopa in suppressing noradrenaline synthesis in sympathetic nerves, seven separate experiments were performed using 122 normotensive male Sprague-Dawley rats and 60 spontaneously hypertensive male Wistar-Okamoto rats. All the experiments yielded similar observations: it was shown that the administration of carbidopa not only blocks the decarboxylation of exogenous L-dopa, but also suppresses the decarboxylation of endogenous dopa formed from 3H-tyrosine within cardiac sympathetic nerve terminals. As a consequence, the drug inhibits noradrenaline synthesis in sympathetic neurons. 11 references.

003331 Yaksh, T. L.; Yamamura, H. I. Department of Anatomy, University College London, London WC1E 6BT, England **Depression by morphine of the resting and evoked release of (3H)-acetylcholine from the cat caudate nucleus in vivo.** Neuropharmacology. 16(4):227-233, 1977.

The effect of systemically administered morphine on the resting and evoked release of (3H)-acetylcholine from the caudate nucleus of the unanesthetized, midpontine pretrigeminally transected cat was studied using the push pull perfusion technique. Morphine resulted in a dose dependent depression of the resting release and of release evoked either by bipolar electrical stimulation of the caudate nucleus or by the administration of excess potassium ion in the perfusate. The antagonism was always reversible by naloxone and in the case of the electrically stimulated release, the antagonism over the dose range used was surmountable with higher stimulation intensities. In several experiments, naloxone reversed the depressant effects of morphine on the evoked release but never on the resting release. The data suggest that morphine can exert a direct effect at a site within the caudate, in the vicinity of the perfusion cannula, as well as one at a site distant from the perfusion site. Whether this depressant effect is upon cholingeric mechanisms directly or indirect through an alternate neurochemical system remains to be determined. 23 references. (Author abstract modified)

003332 Yaksh, Tony L.; Kohl, Randall L.; Rudy, Thomas A. Department of Anatomy and Embryology, University College London, London WC1E 6BT, England **Induction of tolerance and withdrawal in rats receiving morphine in the spinal subarachnoid space.** European Journal of Pharmacology (Amsterdam). 42(3):275-284, 1977.

The induction of tolerance and withdrawal was studied in rats implanted with chronic catheters in the spinal subarachnoid space who were given injections of morphine sulfate, either intrathecally into the lumbar subarachnoid space or intraperitoneally (i.p.). The development of tolerance, as manifested in a reduction of the analgetic efficacy of these injections on the hot plate and tail flick, occurred in a dose dependent fashion over a period of 7 days. At this time, injections of i.p. morphine into animals which had received spinal morphine and vice versa revealed the existence of a two-way cross-tolerance between spinal and systemically administered morphine. Injection of naloxone into the spinal cord of animals exposed to i.p. morphine or conversely, i.p. naloxone in animals tolerant to intrathecal morphine, yielded a hyperreflexia and extreme sensitivity to handling. Other signs commonly observed in precipitated withdrawal, however, such as wet shakes and weight loss, were not observed. 34 references. (Author abstract modified)

003333 Yaksh, Tony L.; Plant, Robert L.; Rudy, Thomas A. University College London, Department of Anatomy, London WCIE 6BT, England **Studies on the antagonism by raphe lesions of the antinociceptive action of systemic morphine.** European Journal of Pharmacology (Amsterdam). 41(4):399-408, 1977.

The effects of lesions in the dorsal/median raphe (DMR), ventral raphe (VR), both dorsal/median and ventral raphe (DMVR), or the reticular formation on the antinociception and catalepsy produced by 3mg/kg, 10mg/kg and 30mg/kg of morphine were studied in rats. The lesions had no significant effect on the catalepsy produced by any of the morphine doses tested. DMR lesions attenuated the antinociceptive action of the 3mg/kg and 10mg/kg doses. VR lesions completely blocked the effects of the 3mg/kg dose and attenuated the effects of the 10mg/kg dose. The combined DMVR lesions produced a total blockade of the 3mg/kg and 10mg/kg doses. None of the lesions produced a significant antagonism of the antinociceptive effects of the 30mg/kg dose. It is suggested that the ascending and descending fiber systems emanating from the dorsal/median and ventral raphe respectively facilitate the expression of morphine induced analgesia but that neither system alone is essential for the manifestation of the antinociceptive effects of systemically administered morphine. 37 references. (Author abstract modified)

003334 Yano, Ichiro; Takemori, A. E. Department of Pharmacology, University of Minnesota, Health Sciences Center, Medical School, Minneapolis, MN 55455 **Inhibition by naloxone of tolerance and dependence in mice treated acutely and chronically with morphine.** Research Communications in Chemical Pathology and Pharmacology. 16(4):721-734, 1977.

Quantification is made of the pharmacological inhibition and/or tolerance to and dependence on morphine when the acute effects of morphine are inhibited in varying degrees by naloxone, to test the postulate that occupation of the morphine receptors by morphine may not be essential for the development of tolerance. The inhibition by naloxone of tolerance and dependence in morphinized mice is dose dependent and time dependent. In animals receiving a single, large dose of morphine, partial inhibition by naloxone of the analgesic effect results in partial development of tolerance and dependence. This relationship appears to be true for animals which have been treated with morphine chronically. Complete and sustained blockage of morphine receptors by naloxone is required for complete inhibition of the development of tolerance and dependence. 19 references. (Author abstract modified)

003335 Yehuda, Shlomo. Department of Psychology, Bar-Ilan University, Tel-Aviv, Israel **Hypothermic effects of antipsychotic phenothiazines.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 137-148).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December 1975, the hypothermic effects of antipsychotic phenothiazines in rats were reported. The drugs tested (chlorpromazine, carphenazine, chlorimpiphenine, chlorprothixene, mepazine, trimepazine, promepazine, perphenazine, thioridazine, thioproperazine, and triflupromazine) produced hypothermia and potentiated rather than blocked dextroamphetamine induced hypothermia. The reported hallucinogenic phenothiazine RP 7630 failed to produce significant hypothermia. Pimozide, but not haloperidol, blocked the hypothermia produced by combinations of dextroamphetamine plus chlorpromazine when administered 30 min prior to dextroamphetamine and 60 min prior to chlorpromazine. It is suggested that the effect of pimozide indicates that dopamine (DA) is involved in the mediation of phenothiazine induced hypothermia. Several possible explanations for the paradoxical findings that both DA receptor blockers and a DA striatal stimulant produce hypothermia are offered. 37 references.

003336 Yoneda, Yukio; Kuriyama, Kinya; Kurihara, Etsuo. Department of Pharmacology, Kyoto Prefectural University of Medicine, Kamikyo-ku Kyoto 602, Japan **Morphine alters distribution of GABA in thalamus.** Brain Research (Amsterdam). 124(2):373-378, 1977.

The effect of acute morphine administration on the distribution of gamma-aminobutyric acid (GABA) in the rat thalamus was examined using a microassay method for GABA. Male Wistar rats were decapitated after administration of morphine or saline, and gross regions of the CNS, cerebellum, medulla, and pons, midbrain, hypothalamus, striatum hippocampus, cerebral cortex, and spinal cord were removed and prepared for assay. There was no significant effect of morphine on GABA contents in cerebellum, medulla and pons, midbrain, hypothalamus, striatum, hippocampus, cerebral cortex, and spinal cord, but a significant increase of GABA content in areas of the thalamus was observed in morphine treated anaimals. Results suggest that functional alterations of GABA containing neurons involved and/or associated with well known pathways for pain perception may play a role in induction of morphine analgesia, possibly by increasing inhibitory inputs at the level of thalamus. 13 references.

003337 Zeller, E. Albert. National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709 **Snake venom action: are enzymes involved in it?** Experientia (Basel). 33(2):143-150, 1977.

The role of enzymes in the action of snake venom is examined. While highly active polypeptides dominate the action of hydrophiid venoms, they appear to play a lesser role in crotalid venom action as compared with enzyme components. Enzymes are involved at many levels of venom action. They serve as spreading agents and produce active agents in the tissues of prey and predators. In several instances some enzymes potentiate the toxic action of others. Therefore, the analysis of a single enzyme may not fully reveal its biofunction. For three enzymes, ophidan L-amino acid oxidase, ATP-pyrophosphatase, and acetylcholinesterase, some of the problems relating to venom toxicity are discussed. Acetylcholinesterase has been found to be closely related to the enzyme present in brain tissue. Its relationship to free acetylcholine bears resemblance to that of the reserpine/MAO relationship. (Author abstract modified)

003338 Zemlan, Frank P.; Trulson, Michael E.; Howell, Russel; Hoebel, Bartley G. Smith Hall, Rockefeller University, New York, NY 10021 **Influence of p-chloroamphetamine on female sexual reflexes and brain monoamine levels.** Brain Research (Amsterdam). 123(2):347-356, 1977.

The effects of parachloroamphetamine (PCA) on sexual reflexes and brain monoamine levels were studied in ovariectomized adult rats. The effect of PCA on female sexual reflexes was biphasic. Administration of PCA to receptive females initially terminated ongoing sexual behavior and this effect was correlated with the release of monoamines, particularly serotonin (5-HT). Sexual reflexes were abolished within 15 min of PCA injection. Other reflexes, including reciprocal forepaw treading, lateral head weaving, hindlimb abduction and Straub tail, were elicited by PCA. Long-term administration of PCA produced facilitation of female sexual behavior accompanied by a relatively specific dose dependent depletion of 5-HT, with both dopamine and norepinephrine levels being far less affected. This long-term facilitation of female sexual reflexes was not blocked by dexamethazone suggesting that PCA acts directly on the neural substrate for mating and does not produce its facilitation via adrenal progesterone. This biphasic influence of PCA on mating reflexes, paralleling its effect on monoamine transmission, suggests serotonergic involvement in the integration of mating behavior. 38 references. (Author abstract modified)

003339 Zimmerman, Selma; Zimmerman, Arthur M.; Cameron, Ivan L.; Laurence, Helen L. Div. of Natural Sciences, Glendon college, York University **Delta1-tetrahydrocannabinol, cannabidiol and cannabinol effects on the immune response of mice.** Pharmacology (Basel). 15(1):10-23, 1977.

The effects of delta1-tetrahydrocannabinol, cannabidiol, and cannabinol on the immune response of 47 3 week old male mice stimulated with sheep red blood cells were studied. The mice were given 4 daily intraperitoneal doses of either drug or vehicle (Tween 80-propylene glycol in 1% saline) or a single injection of sheep red blood cells in addition to 4 daily doses of vehicle or 1, 5, or 10mg tetrahydrocannabinol/kg, 25mg cannabidiol/kg, or 25mg cannabinol/kg. Tetrahydrocannabinol elicited a dose dependent depression of the immune response. The impairment of humoral immunity was specific for tetrahydrocannabinol, but not for cannabidiol or cannabinol. Suppression of the antigenic response by tetrahydrocannabinol

was reflected as a reduction of splenic weight, reduction in the number of splenic antibody forming cells, lowered hemagglutination titer, and reduction in the percentage of splenic white pulp to total spleen volume. 30 references. (Author abstract modified)

003340 Zweig, Jonathan S.; Castagnoli, Neal, Jr. Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, CA 94143 **In vitro o-demethylation of the psychomimetic amine, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane.** Journal of Medicinal Chemistry. 20(3):414-421, 1977.

The in vitro O-demethylation of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP) was carried out in order to investigate the possible relationship between metabolism and psychomimetic activity among the methoxylated 1-phenyl-2-aminopropanes. Employing a sensitive and highly selective stable isotope dilution assay, it was observed that rabbit liver homogenates biotransform the parent compound to its 2-O-demethyl, 5-O-demethyl, and bis (O-demethyl) metabolites. Both monophenolic metabolites are enriched in their S enantiomers. The bis (O-demethyl) metabolite has structural, chemical, and electrochemical similarities to the sympatholytic agent 6-hydroxydopamine. The possible significance of metabolic O-demethylation in terms of the psychomimetic properties of the parent compound is discussed. 44 references. (Author abstract modified)

04 MECHANISM OF ACTION: BEHAVIORAL

003341 Andry, Diane K.; Horita, A. Department of Pharmacology, School of Medicine, University of Washington, Seattle, WA 98195 **Thyrotropin-releasing hormone : physiological concomitants of behavioral excitation.** Pharmacology Biochemistry and Behavior. 6(1):55-59, 1977.

The time course of several physiological measures of thyrotropin releasing hormone (TRH) narcosis reversal was investigated and the effects of TRH on control rabbits were delineated. Two doses (10 ug and 100 ug) of thyrotropin releasing hormone (TRH) or saline were injected intraventricularly in rabbits pretreated with either saline, pentobarbital or phenobarbital. Behavior, EEG patterns, respiration rate and heart rate were monitored for 100 min posttreatment. TRH significantly altered all physiological indices except heart rate in both barbiturate and saline pretreated animals. The results support the contention that TRH modified central functioning by direct action. Results are discussed in terms of barbiturate antagonism and excitatory effects of TRH. 15 references. (Journal abstract modified)

003342 Annau, Zoltan. Department of Environmental Health Sciences, Johns Hopkins University, 615 North Wolfe St., Baltimore, MD 21205 **The effect of carbonic anhydrase inhibition on electrical self stimulation of the brain during hypoxia.** Life Sciences. 20(6):1043-1050, 1977.

The effects of a carbonic anhydrase inhibitor, (2-benzenesulfonamido-1,3,4-thiadiazole-5-sulfonamide, CL 11,366,) (BSTS) on electrical self-stimulation of the rat brain was studied during hypoxia. Rats implanted with electrodes in the lateral hypothalamus were trained to self-stimulate. Both controls and rats pretreated with BSTS declined in performance in hypoxia (8% oxygen). One hour after the onset of 8% oxygen, the BSTS treated rats responded at a significantly higher rate than controls. Arterial samples from arterial catheters showed that the BSTS treated rats had a significantly lower pH than the controls both in air and hypoxia, but there were no significant changes in pCO2 or pO2. The results suggest that the actions of BSTS may be rather complex and changing over time. The improved performance during hypoxia of subjects treated with carbonic anhydrase inhibitors may be the result of the concurrent acid base changes and altered catecholamine activity in the brain. 22 references.

003343 Antelman, Seymour M.; Edwards, David J.; Lin, Marina. Department of Psychiatry, Univ. of Pittsburgh Medical School, Pittsburgh, PA 15260 **Phenylethylamine: evidence for a direct, postsynaptic dopamine-receptor stimulating action.** Brain Research (Amsterdam). 127(2):317-322, 1977.

To study the action of phenylethylamine (PE) in the nigrostriatal dopamine (DA) pathways, a series of experiments with 6-hydroxydopamine (6-OHDA) lesioned rats was undertaken utilizing the rotational behavior paradigm developed by Ungerstedt. PE treatment produced contralateral apomorphine-like rotation. Striatal assays indicated a 98% depletion of DA in the striatum ipsilateral to the 6-OHDA injection and a 67% depletion on the uninjected side. All animals displayed unidirectional rotation in a second experiment following slow injection of 6-OHDA. All animals tested with PE and alpha-methyltyrosine (AMT) reversed their directional preference and showed contralateral turning. Retest with PE alone resulted in a reversion to previous behavior patterns. Results suggest that PE can act to stimulate striatal DA receptors directly, although its presynaptic DA releasing action may predominate. It is noted that PE has recently been implicated in several disorders including depression, migraine headaches, and in theory, in schizophrenia. A further study of homovanillic acid levels in intact PE treated animals is briefly presented. 15 references.

003344 Babbini, M.; Gaiardi, M.; Bartoletti, M. Instituto di Farmacologia, Universita di Bologna, Via Irnerio, 48, I-40126 Bologna, Italy **Anorexic and behavioural effects of a new imidazo-isoindole derivative (mazindol) in comparison with d-amphetamine in the rat.** Pharmacology (Basel). 15(1):46-56, 1977.

The effects of mazindol (animidazo-isoindole derivative) and d-amphetamine on motor and feeding activity and on avoidance behavior were compared in male rats. It was found that both drugs depress feeding activity in a dose related manner and increase the motor activity of the animals. However, the ratio of the lowest motility increasing dose and the lowest appetite suppressant dose is 0.5for d-amphetamine and 2 for mazindol. Mazindol, like d-amphetamine, caused a stereotyped behavior in rats when given in very high doses, but the range between the anorexic and the stereotyped behavior dose is much higher for mazindol than for d-amphetamine. The shuttlebox avoidance behavior suppressed by tetrabenazine is completely restored by d-amphetamine and partially by mazindol. Lever pressing avoidance suppressed by tetrabenazine is restored by d-amphetamine while mazindol at the doses used is ineffective. It is concluded that mazindol could be an anorexic agent better suited than d-amphetamine for clinical use. 20 references. (Author abstract modified)

003345 Baez, Luis A.; Kerns, Robert D.; Smith, Paul. Psychopharmacology Laboratory, Department of Psychology, Southern Illinois University, Carbondale, IL 62901 **Lack of stimulation by high amphetamine doses following a low dose of spiperone.** European Journal of Pharmacology (Amsterdam). 41(1):77-79, 1977.

The locomotor stimulant effect and stereotypic effects of amphetamine were investigated in rats pretreated with the

specific dopaminergic blocker spiperone. Amphetamine in doses from 8mg/kg to 64mg/kg failed to produce consistent, significant behavioral responses after spiperone treatment. The possibility that spiperone acts by noncompetitive antagonism of amphetamine at dopaminergic synapses is suggested. 7 references. (Author abstract modified)

003346 Baker, T. B.; Cannon, D. S.; Berman, R. F.; Atkinson, C. A. Alchohol Research Program, Veterans Administration Hospital, Salt Lake City, UT 84113 **The effect of diet on ethanol withdrawal symptomatology.** Addictive Behaviors. 2(1):35-46, 1977.

Experiments with 82 Long-Evans rats were conducted to test the effect of nourishment on tolerance of ethanol dosages and creation of ethanol dependency. Nourished rats were able to tolerate up to 25% higher ethanol dosages than were nutrient deprived rats. Nourished subjects were also less prone to withdrawal seizures. Deprived rats showed higher blood ethanol content than nourished rats receiving equivalent ethanol doses, but comparable to that of nourished rats receiving 25 to 30% more ethanol. 37 references. (Author abstract modified)

003347 Barr, Gordon A.; Gibbons, Judith L.; Bridger, Wagner H. Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461 **Inhibition of rat predatory aggression by acute and chronic D- and L-amphetamine.** Brain Research (Amsterdam). 124(3):565-570, 1977.

Inhibition of predatory aggression (mousekilling) in rats by acute and chronic D-amphetamine and L-amphetamine was studied in terms of the relative ability of each isomer to inhibit mousekilling and in terms of the development of tolerance and cross-tolerance to the two isomers. Both forms inhibited mousekilling when tested at 20 or 60 minutes after an acute injection in a direct dose related manner. Attack latencies correlated highly with the kill latencies and showed the same inhibition by amphetamine. At both time intervals after injection, D-amphetamine was about 1.5times as potent as L-amphetamine in inhibiting the response. Tolerance developed to the inhibition of killing by D-amphetamine but not to inhibition induced by L-amphetaime. It is suggested that a reason for this difference lies in a possible mechanism that involves noradrenergic mechanisms but does not involve dopaminergic systems. It is concluded that, while the present data are consistent with the hypothesis that increased catecholamine function inhibits predation, there are probably other neurotransmitter systems involved in mousekilling behavior. 26 references. (Author abstract modified)

003348 Belknap, J. K.; Ondrusek, G.; Berg, J.; Waddingham, S. Department of Psychology, University of Texas at Austin, Austin, TX 78712 **Barbiturate dependence in mice: effects of continuous vs. discontinuous drug administration.** Psychopharmacology (Berlin). 51(2):195-198, 1977.

An investigation was carried out in mice to determine the effects of continuous administration vs. discontinuous administration of phenobarbital (PB) on the resulting degree of functional tolerance and physical dependence development and to examine the relationship between functional tolerance and physical dependence. Three groups of mice received continuous exposure to PB for 3, 6, or 9 days; two other groups had one or two 24 h drug free periods interpolated among the 6 or 9 days of PB consumption. The discontinuous schedule significantly attenuated the development of physical dependence as determined by the severity of withdrawal symptoms. Functional tolerance development was also attenuated in a manner that closely paralleled the effects on physical dependence development. The five group means showed a perfect rank order correlation between functional tolerance and physical dependence development. 15 references. (Author abstract modified)

003349 Bergmann, F.; Altstetter, R.; Pasternak, V.; Chaimovitz, M.; Oreg, M.; Roth, D.; Hexter, C.; Wilchek, M. The Hebrew University-Hadassah Medical School, Jerusalem, Israel **Cerebral application of enkephalins.** Experientia (Basel). 33(2):217, 1977.

The effect of the application of extrinsic enkephalins (polypeptides with morphine-like activity) to the cerebral tissue of rats in vivo was tested. Enkephalins were injected or implanted into the ventral thalamus or lateral ventricle of rats. The rats exhibited only weak signs of stereotypic behavior such as rubbing and licking, but which did not progress to gnawing. Results indicate that the survival of extrinsic enkephalins in cerebral tissue is not sufficiently prolonged to evoke morphine induced gnawing. 7 references. (Author abstract modified)

003350 Bert, J.; Saier, J.; Tognetti, P.; Toure, M. F. no address **/Effect of chlorimipramine on the so called Ponto-Geniculo-Occipital activity (PGO) in a primate, Papio hamadryas./** Effet de la chlorimipramine sur l'activite de pointes "Ponto-Geniculo-Occipitales" (PGO) du babouin Papio hamadryas. Psychopharmacology (Berlin). 51(3):301-304, 1977.

The effects on sleep, particularly Ponto-Geniculo-Occipital (PGO) activity, of daily injections of chlorimipramine were observed in three hamadryas adult female baboons. The effects were nearly identical with the effects observed in man. PGO activity, recorded in the lateral geniculate nucleus, was much disturbed. The total number of PGO fell downward from the first recording, and the number of PGO/minute during paradoxial sleep was even more decreased. The data suggest a selective influence of chlorimipramine on the mechanisms of PGO activity. The question of whether this effect is of importance to the treatment of depression symptoms is discussed. 7 references. (Journal abstract modified)

003351 Best, Michael R.; Batson, John D. Department of Psychology, Southern Methodist University, Dallas, TX 75275 **Enhancing the expression of flavor neophobia: some effects of the ingestion-illness contingency.** Journal of Experimental Psychology: Animal Behavior Processes. 3(2):132-143, 1977.

The degree to which neophobia can be modified by toxicosis, the conditions under which the contingency between ingestion and illness enhances neophobia, and the manner in which previously learned aversions mediate subsequent enhanced neophobias were studied in five experiments with 139 rats poisoned by the administration of lithium chloride. Rats administered lithium chloride following ingestion of a novel coffee solution showed an enhanced neophobia reaction to vinegar and casein. This enhancement was specific to the novelty of both the conditioning and test fluids and was not observed in animals receiving noncontingent toxicosis. Poisoning alone, however, mediated a nonspecific fluid suppression that persisted for approximately two drinking sessions following treatment. In contrast to other experiments, the operation of generalization was detected only when a novel flavor was the test fluid, suggesting that neophobia enhancement is at least partially mediated by a conditioned novelty aversion resulting from the novel flavor/lithium contingency. 23 references. (Author abstract modified)

003352 Bhargava, Hemendra N. Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois Medical Center, Chicago, IL 60612 **Opiate-like action of methionine-enkephalin in inhibiting morphine abstinence syndrome.** European Journal of Pharmacology (Amsterdam). 41(1):81-84, 1977.

The effects of intracerebroventricular administration of methionine-enkephalin were compared with those of intracerebroventricular administration of morphine in preventing naloxone precipitated withdrawal jumping in morphine dependent mice. Both drugs inhibited the withdrawal jumping response, but neither drug inhibited withdrawal defecation or rearing behavior. Morphine sulfate was four times as potent as methionine-enkephalin, on a molar basis, in inhibiting the syndrome. The data provide new in vivo pharmacologic evidence for the opiate-like action of the endogenous substrance methionine-enkephalin. 15 references. (Author abstract modified)

003353 Bhargava, Hemendra N. Dept. of Pharmacognosy, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612 **Rapid induction and quantitation of morphine dependence in the rat by pellet implantation.** Psychopharmacology (Berlin). 52(1):55-62, 1977.

Adult male rats were administered morphine pellets by subcutaneous implantation in four distinct time dosage schedules to investigate rate of inducfion and quantification of morphine dependence. The results suggest that it is possible to produce a high degree of physical dependence on morphine in a short time period by pellet implantation. Of the schedules employed, administration of 4 morphine pellets over a 3-day period produced the lowest degree of dependence on morphine, whereas administration of 10 pellets over a 10-day period produced the highest. Dependence was measured by the dose of naloxone required to produce a stereotyped jumping response. Abrupt withdrawl of morphine by pellet removal as well as naloxone precipitated withdrawal resulted in body weight loss and initial hyperthermic effects followed by hypothermic response. A correlation was found to exist between the naloxone dose required to produce the jumping response, body weight loss, and hypothermia during naloxone induced withdrawal in morphine dependent rats. It is suggested that in studies attempting to correlate altered biochemical mechanisms in the central nervous system and morphine dependence or withdrawal, it is highly important to first establish the degree of morphine dependence. 22 references.

003354 Biggio, G.; Della Bella, D.; Frigeni, V.; Guidotti, A. Department of Pharmacology, University of Cagliari Medical School, Cagliari, Italy **Potentiation of morphine analgesia by muscimol.** Neuropharmacology (Oxford). 16(2):149-150, 1977.

The effect of muscimol, an analogue of gamma-aminobutyric acid (GABA) which activates GABA receptors in the brain, on morphine induced analgesia was studied in rats and mice. Muscimol failed to cause analgesia when given alone but lowered the estimated dosage (ED50) for morphine analgesia significantly when given intravenously prior to the morphine. The mechanism whereby this potentiation of analgesia takes place is undetermined. 9 references.

003355 Blum, K.; Wallace, J. E.; Meyer, Eleanor; Schwertner, H. A. University of Texas, Health Science Center at San Antonio, San Antonio, TX 78284 **Intensification of amphetamine-induced excitation by methysergide, a serotonergic receptor blocker.** Experientia (Basel). 33(2):213-215, 1977.

Methysergide, a serotonergic receptor blocker, was studied to determine its effects against d-amphetamine induced excitation as measured by convulsions elicited by handling in mice. Significant intensification of the action of d-amphetamine was observed. It is suggested that the understanding of the behavioral effects of amphetamine should take into account the role of the serotonergic system in the central action of amphetamine. 20 references. (Author abstract modified)

003356 Bohus, B. Rudolf Magnus Institute for Pharmacology Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands **Effect of desglycinamide-lysine vasopressin (DG-LVP) on sexually motivated T-maze behavior of the male rat.** Hormones and Behavior. 8(1):52-61, 1977.

The effect of desglycinamide lysine vasopressin (DG-LVP), a vasopressin analog that has been found to facilitate the maintenance of active and passive avoidance behavior, on the retention of a sexually motivated choice behavior in a T-maze was studied in 48 male rats. A higher percentage of rats receiving DG-LVP after each acquisition session showed a correct choice during free choice retention trials, and the total number of correct choices was higher than in controls. Copulation reward after a correct choice was an essential requisite for acquiring the choice response and retention effect of DG-LVP. Males that were prevented from copulating with the receptive female goal rat or that were presented with another male in the goal box did not acquire the response, and their behavior was not influenced by DG-LVP. Response latencies were never affected by the peptide. It is concluded that the long-term effect of vasopressin on learned behavior is of a rather general nature and is most probably due to facilitated memory consolidation processes. 21 references. (Author abstract)

003357 Braestrup, C. Psychopharmacological Research Laboratory, Sct. Hans Hospital, Dept. E., DK-4000 Roskilde, Denmark **Changes in drug-induced stereotyped behavior after 6-OHDA lesions in noradrenaline neurons.** Psychopharmacology (Berlin). 51(2):199-204, 1977.

The effects of 6-hydroxydopamine (6 OHDA) induced bilateral lesions in the ascending noradrenaline (NA) neurons, lateral to the medial raphe nucleus, on drug induced stereotyped behavior were examined in rats. Dopamine neurons and 5-hydroxytryptamine neurons were not affected by the lesions. Dextroamphetamine induced stereotyped behavior and phenethylamine hydrochloride induced stereotyped behavior were altered by the lesions so that licking behavior was increased while biting/gnawing behavior was rarely induced. These effects were partially antagonized by the NA reuptake inhibitor protriptyline. It is suggested that there is a noradrenergic influence on the behavioral expression of dopaminergically mediated stereotyped behavior. 32 references. (Author abstract modified)

003358 Brower, Kirk J.; Siegel, Ronald K. Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA 90024 **Hallucinogen-induced behaviors of free-moving chimpanzees.** Bulletin of the Psychonomic Society. 9(4):287-290, 1977.

The effects of the hallucinogen N,N-dimethyltryptamine (DMT) on the social behavior of two island groups of four champanzees each were studied. One target animal from each group was selected for treatment and individual and social behaviors were scored according to a quantitative observational system. Low doses of DMT (.5to 3.0mg/kg) caused dose dependent increases in duration of vocalization, fear grimace,

and locomotion. Higher doses (4.0mg/kg) tended to decrease these behaviors as well as others such as self-grooming. Social aggregation tended to decrease with increasing doses, and social interactions between target animals and others were rare. Results tended to support the hypothesis that hallucinogens increase social spacing and isolation. 19 references. (Author abstract)

003359 Cannon, D. S.; Baker, T. B.; Berman, R. F. Alcohol Research (3D), VA Hospital, Salt Lake City, UT 84148 **Taste aversion disruption by drug pretreatment: dissociative and drug-specific effects.** Pharmacology Biochemistry and Behavior. 6(1):93-100, 1977.

Dissociative and drug specific effects were studied in taste aversion disruption by lithium or ethanol pretreatment in rats. Disruption of taste aversion learning following the administration of the same drug prior to and during conditioning (intra/agent disruption) was shown to be greater than disruption following the administration of one drug prior to conditioning and another during conditioning (inter/agent disruption). Comparable dosages of ethanol and lithium chloride served as unconditioned stimuli. Inter/agent disruptions are attributed to a dissociation of conditioned and unconditioned stimuli, while intra/agent disruptions are attributed to both a dissociative effect and drug/specific effects. Intra-agent disruption was correlated with an independent measure of tolerance, suggesting tolerance constitutes at least a portion of the drug/specific effects. 31 references. (Journal abstract modified)

003360 Cappell, Howard; Le Blanc, A. E. Addiction Research Foundation, 33 Russell Street, Toronto, Ontario M5S 2S1, Canada **Parametric investigations of the effects of prior exposure to amphetamine and morphine on conditioned gustatory aversion.** Psychopharmacology (Berlin). 51(3):265-271, 1977.

Two experiments, massed versus spaced exposure to morphine and amphetamine (180 rats), and loss rate of the effects of prior exposure to morphine (120 rats), were conducted to determine the effects of prior exposure on conditioned gustatory aversion. Pretreatments with morphine or amphetamine massed at 24 hour intervals were no more effective in attenuating conditioning than pretreatments spaced at 120 hour intervals, but pretreatment with morphine provided more persistent protection against subsequent conditioning by itself than did amphetamine. The similarity of massed and spaced pretreatment effects can be interpreted without appealing to tolerance as a factor, but the greater persistence of morphine pretreatment implicates tolerance as a mechanism. 14 references. (Author abstract modified)

003361 Carney, John M. Dept. of Pharmacology, Medical College of Virginia, Richmond, VA 23298 **Pargyline-induced increases in sensitivity to the effects of drugs on operant behavior in pigeons.** Psychopharmacology (Berlin). 52(1):97-102, 1977.

Acute doses of pargyline were given to male pigeons (N=6) immediately prior to testing of responding on a multiple fixed-interval, fixed-ratio schedule of food reinforcement to investigate the sensitivity of operant responding to the effects of morphine and a series of sympathomimetic amines during administration of a monoamine oxidase (MAO) inhibitor. Acute doses of pargyline decreased responding and daily administration initially decreased responding. Tolerance developed so that after 4 days of daily pargyline, responding had returned to control values. Chronic pargyline resulted in an enhanced sensitivity to the effects of d-amphetamine, ephedrine, tyramine, and morphine on schedule controlled responding. Both d-amphetamine and pentobarbital increased fixed-interval responding at relatively low doses, while higher doses decreased responding. Daily pargyline resulted in an increased sensitivity to both the increases and decreases in response rates produced by d-amphetamine. In contrast, sensitivity to pentobarbital was not changed after daily pargyline. Ephedrine, tyramine, and morphine only decreased fixed-interval responding. Chronic pargyline resulted in an increased sensitivity to the response rate decreasing effects of ephedrine, tyramine, and morphine. In addition to the increased sensitivity of fixed-interval responding to the effects of tyramine, the dose effect curve for fixed-ratio responding was also shifted to the left. Since tyramine is a good substrate for MAO, it is suggested that some of the shift to the left may have been due to an inhibition of tyramine metabolism. 36 references. (Author abstract modified)

003362 Castellano, Claudio. Laboratory of Psychobiology and Psychopharmacology, Via Reno, 1, Rome, Italy **Effects of pre- and post-trial caffeine administrations on simultaneous visual discrimination in three inbred strains of mice.** Psychopharmacology (Berlin). 51(3):255-258, 1977.

Three inbred strains of mice (BALB/cJ, DBA/2J, and C57BL/6J) mice were tested after pretrial and posttrial caffeine injections in the five choice Yerkes-Thompson Bryant-Bovet Nitti apparatus for visual patterns discrimination in two sets of experiments. In the first experiment, the patterns were opposite oriented oblique bars, and, in the second experiment, the patterns were U-shaped figures, one opened towards the right, the other opened towards the left. The control BALB mice showed the highest learning abilities of the three control groups. In the first experiment, the performance of the control C57 and DBA mice was similar: in the second experiment, the control C57 mice performed at the lowest level. Posttrial and postrial caffeine administrations were followed by performance impairment in the BALB strain, while performance improvements were evident in the drugged animal of the other two strains. 10 references. (Author abstract modified)

003363 Colasanti, Brenda K. Department of Phamacology, West Virginia University Medical Center, Morgantown, WV 26506 **Involvement of brain biogenic amines in the electroencephalographic and behavioural effects of morphine in post-addict rats.** Neuropharmacology. 16(4):235-240, 1977.

The involvement of brain biogenic amines in electroencephalographic (EEG) and the behavioral effects of morphine in postaddict rats were studied. Morphine administration to postaddict rats abstinent for 7 days was followed by the immediate appearance of EEG desynchronization and marked behavioral hyperarousal. After pretreatment of rats with alpha-methyl-p-tyrosine (MPT), p-chlorophenylalanine (CPA), or a combination of the two during the period of morphine addiction and withdrawal, the EEG and behavioral effects of morphine given on the 8th day of abstinence were unaltered. Brain levels of the catecholamines, norepinephrine (NE) and dopamine (DA), measured in untreated postaddict rats after a morphine test dose also remained unchanged. Brain levels of serotonin were significantly elevated 30 min after the morphine challenge. Determination of brain NE and DA levels made 30 min after injection of morphine to postaddict rats pretreated with MPT showed a reduction in brain DA utilization. The results suggest that both dopaminergic and serotonergic brain pathways may be involved in the mediation of EEG and behavioral responses to morphine on postaddict rats. 36 references. (Author abstract modified)

003364 Colpaert, Francis C.; Niemegeers, C. J. E.; Janssen, P. A. J. Department of Pharmacology, Janssen Pharmaceutica Research Laboratories, B-2340 Beerse, Belgium **Haloperidol blocks the discriminative stimulus properties of lateral hypothalamic stimulation.** European Journal of Pharmacology (Amsterdam). 42(1):93-97, 1977.

The effects of haloperidol on the discriminative stimulus properties of an internal stimulus, i.e. electrical stimulation of the lateral hypothalamus (LH) was studied in rats trained to discriminate LH stimulation from its absence. Haloperidol blocked the internal stimulus induced by stimulation of the LH and the block was inversely related to the strength (train frequency) of the stimulus. The results support the hypothesis that an internal stimulus with reinforcing properties can be effectively applied as a discriminative stimulus, and that the presumed blockade of the reinforcing properties of the stimulus entails blockade of its discriminative and reinforcing properties of stimuli exerting control of behavior. 11 references.

003365 Connelly, John F.; Connelly, Jacqueline M.; Nevitt, James R. Department of Psychology, Kansas State College of Pittsburg, Pittsburg, KS 66762 **Effect of foot-shock intensity on amount of memory retrieval in rats by emotionally important stimuli in a drug-dependent learning escape design.** Psychopharmacology (Berlin). 51(2):153-157, 1977.

The relationship between footshock intensity and the ability of a paired auditory stimulus to act as a memory prompter during nonshock test trials was investigated in rats trained to escape footshock in a drug dependent learning (DDL) regimen while receiving chlordiazepoxide. The rats subsequently responded randomly on nonshock test trials while in the nondrug state, but continued to respond significantly above random level when in the drug state. Four transfer groups were also trained in the drug state, but with an auditory stimulus presented simultaneously with footshock. Each transfer group received a different footshock intensity during training. The auditory tone continued to be sounded during testing with no footshock. The percentage of correct turns, first trial correct turns, and latency scores were significantly different from the DDL group's performance. The results are interpreted as demonstrating that an emotionally important auditory stimulus can initiate a memory retrieval process that can overcome a physiological state. This memory retrieval process was not modified by wide variations in footshock intensity. 11 references. (Author abstract modified)

003366 Consroe, Paul; Martin, Parthena; Eisenstein, Douglas. Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ 85721 **Anticonvulsant drug antagonism of delta9-tetrahydrocannabinol-induced seizures in rabbits.** Research Communications in Chemical Pathology and Pharmacology. 16(1):1-13, 1977.

The effects of standard anticonvulsants on delta9-tetrahydrocannabinol (dTHC) induced behavioral convulsions were studied in rabbits. A population of New Zealand White rabbits exhibited such convulsions when given low doses of psychoactive cannabinoids of marijuana, (dTHC). Carbamazepine, diazepam, and phenytoin were most effective in blocking these convulsions, and phenobarbital and ethosuximide also blocked convulsions but only at toxic doses. Cannabidiol was effective in blocking convulsions when given concurrently with, but not prior to, dTHC. It is concluded that these cannabinoid sensitive rabbits provide a model for studying the mechanism of dTHC action. 24 references. (Author abstract modified)

003367 Cools, A. R.; Broekkamp, C. L. E.; Gieles, L. C. M.; Megens, A.; Mortiaux, H. J. G. M. Department of Pharmacology, University of Nijmegen, Geert Grooteplein Noord 21, Nijmegen, The Netherlands **Site of action of development of partial tolerance to morphine in cats.** Psychoneuroendocrinology (Oxford). 2(1):17-33, 1977.

The site of action of development of partial tolerance to morphine was studied in cats by examining the effects of the intracranial injection into the nucleus linearis intermedius raphe (NRL) of L-noradrenaline (NA), L-propranolol (P), and desglycinamide lysine-8-vasopressin (DG-LVP) on morphine induced behavior. The complex behavioral syndrome elicited in cats by morphine, which is built up in 3 steps: 1) depression phase; 2) reorganization phase; and 3) ritualization phase, was modified by the daily administration of morphine; the onset of the reorganization and ritualization phase was retarded from the 3rd day. Injection of NA during the ritualization phase triggered by a single injection of morphine inhibited ritualization, whereas comparable treatment with P potentiated ritualization. However, pretreatment with NA and P prior to morphine potentiated and suppressed, respectively, the display of stereotyped and ritualized patterns. Administration of DG-LVP during the ritualization phase potentiated the phase, but pretreatment with DG-LVP produced effects characteristic of chronic treatment with morphine. The results provide evidence in favor of the concept that characteristic changes within the NRL, in particular, changes in the noradrenergic fiber system terminating within the structure, are essential prerequisites for the development of partial tolerance to morphine induced behavior in cats. 51 references.

003368 Costall, Brenda; Marsden, C. David; Naylor, Robert J.; Pycock, Christopher J. Postgraduate School of Studies in Pharmacology, University of Bradford, Bradford, England **Stereotyped behaviour patterns and hyperactivity induced by amphetamine and apomorphine after discrete 6-hydroxydopamine lesions of extrapyramidal and mesolimbic nuclei.** Brain Research (Amsterdam). 123(1):89-111, 1977.

Changes in stereotyped sniffing, biting, and hyperactivity induced by apomorphine and d-amphetamine in the rat were determined after bilateral 6-hydroxydopamine (6-OHDA) lesions of the extrapyramidal caudate putamen (CP) (anterior and center), globus pallidus (GP) and substantia nigra (SN), the mesolimbic nucleus accumbens (ACB), tuberculum olfactorium (TUO) and central amygdaloid nucleus (ACE). Lesions were also induced in the medial forebrain bundle in the lateral hypothalamus (LH). The 6-OHDA lesions of the CP reduced amphetamine biting but not sniffling or hyperactivity. Centrally placed 6-OHDA failed to modify any response to apomorphine but anterior locations reduced apomorphine biting. Both lesion locations led to a reduction in striatal dopamine (DA) content. 6-OHDA lesions of the GP reduced striatal DA but initially potentiated before reducing both apomorphine and amphetamine biting. The LH and SN lesions reduced striatal and mesolimbic DA and potentiated apomorphine biting. The LH lesions reduced amphetamine biting and hyperactivity but the SN lesions initially potentiated these responses. 6-OHDA lesions of the ACB reduced the DA content of this nucleus but had little effect on the TUO. These lesions reduced the duration of amphetamine hyperactivity and potentiated apomorphine biting. Equally selective lesions of the TUO enhanced the locomotor activity response to both apomorphine and amphetamine. Lesions of the ACE depleted amygdaloid DA and reduced or abolished apomorphine and amphetamine biting in the chronic stage. The results indicate that the sites for mediation of stereotyped sniffling, biting or

hyperactivity are not the same for apomorphine and amphetamine, and that each behavioral state involves the functioning of more than one DA containing area. 55 references. (Author abstract modified)

003369 Dantzer, Robert. I.N.R.A., Station of Pharmacology, 180, Chemin de Tournefeuille, F-31300 Toulouse, France **/Effects of diazepam on exploratory behavior of pigs./** Etude des effets du diazepam sur le comportement explorateur du Porc. Psychopharmacology (Berlin). 51(3):317-321, 1977.

The effect of diazepam on the exploratory behavior of 20 pigs was studied in two successive 20 minute sessions in a two compartment box by counting the number of crossings from one compartment to the other and observing the activity patterns. Injection of 1mg/kg diazepam before the first session increased the number of crossings without affecting the temporal decline of activity within the session; treated pigs did not attempt to escape the experimental situation and tended to be more perseverative in their activity patterns than control pigs. Injected before the second session, diazepam did not modify the exploratory behavior. There was no evidence of a state dissociation effect in experimental groups for which the treatment condition differed from one session to the other. The results are discussed with respect to current theories about the behavioral effects of benzodiazepines. 18 references. (Journal abstract modified)

003370 Dantzer, Robert. Laboratorie de Pharmacologie, 180 chemin de Tournefeuille, F-31300 Toulouse, France **Effects of diazepam on behaviour suppressed by extinction in pigs.** Pharmacology Biochemistry and Behavior. 6(2):157-161, 1977.

The effects of diazepam on behavior suppressed by extinction was studied in 21 pigs. Diazepam injected in pigs previously trained to perform an operant response for food according to a continuous reinforcement schedule significantly increased resistance to extinction compared to control pigs. In pigs submitted to a time out procedure, diazepam increased the number of nonreinforced responses at the beginning of the acquisition but was unable to disinhibit suppressed behavior in the later stages of acquisition when the extinguished behavior was well acquired. Results are discussed with respect to antiaverse or disinhibitory effects of benzodiazepines, and an alternative interpretation, the strengthening of the prevailing behavioral tendency in the animal's repertoire at the time of the test, is suggested. 28 references. (Author abstract)

003371 Davis, Michael; Cedarbaum, Jesse M.; Aghajanian, George K.; Gendelman, David S. Dept. of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508 **Effects of clonidine on habituation and sensitization of acoustic startle in normal, decerebrate and locus coeruleus lesioned rats.** Psychopharmacology (Berlin). 51(3):243-253, 1977.

The time course and dose response effects of clonidine on startle in rats, the way the alpha-adrenergic antagonists, phentolamine and piperoxane, might alter the effects of clonidine on startle, whether clonidine would still affect startle in acutely decerebrate rats and rats with bilateral lesions of the locus coeruleus, and whether clonidine depresses startle by interfering with its motor aspects or by reducing sensitization to background noise or by accelerating rate of startle habituation were investigated. Clonidine potently depressed startle amplitude and the effect was monotonically related to dose. Pretreatment with piperoxane antagonized this effect but pretreatment with phentolamine did not. Clonidine still depressed startle in acutely decerebrate rats and in rats with bilateral ablation of the locus coeruleus. Clonidine did not interfere with sensitization to background noise and did not interfere with the ability to startle but instead improved within session habituation. Clonidine appears to be one of the few drugs which improves habituation without directly interfering with the ability to respond. The possibility that clonidine might affect startle by stimulating central epinephrine rather than norepinephrine receptors is discussed. 46 references. (Author abstract modified)

003372 Davis, Michael; Gallager, Dorothy W.; Aghajanian, George K. Yale University School of Medicine, New Haven, CT 06508 **Tricyclic antidepressant drugs: attenuation of excitatory effects of d-lysergic acid diethylamide (LSD) on acoustic startle response.** Life Sciences. 20(7):1249-1258, 1977.

The attenuation of excitatory effects of d-lysergic acid diethylamide (LSD) on acoustic startle response in rats by the tricyclic antidepressant drugs chlorimipramine (CIMI), desipramine (DMI), imipramine (IMI), and chlordesipramine (C-DMI) was studied. All four drugs blocked the excitatory effects of a low dose of LSD on the acoustic startle response. Over a dose range from 1 to 5mg/kg, CIMI and DMI were about equally potent in blocking the LSD effect, despite the fact that both drugs actually increased brain levels of LSD. In contrast, alpha-methyl-p-tyrosine did not block the effect of LSD on startle. By themselves, DMI, IMI and C-DMI increased startle amplitude 20 to 30% whereas CIMI alone had no effect on startle. The ability of CIMI and IMI to block the excitatory effect of LSD on startle is consistent with the hypothesis that prior cessation of raphe cell firing caused indirectly by these drugs with no resultant change in 5-HT availability should preempt the ability of LSD to increase startle by directly inhibiting raphe cell firing and decreasing 5-HT availability. Inhibiting raphe cell firing and decreasing 5-HT availability. The finding that the other tricyclics also block the effect of LSD is not explained by that hypothesis. Results are discussed in terms of the serotonin hypothesis of the action of hallucinogenic drugs on behavior. 33 references. (Author abstract modified)

003373 De Obaldia, Ricardo; Magnuson, Debra J.; Reid, Larry D. Bradley University, Peoria, IL 61606 **Addictive agents and intracranial stimulation: daily amphetamine and hypothalamic self-stimulation.** Bulletin of the Psychonomic Society. 9(5):377-379, 1977.

To examine the effects of daily amphetamine on lever pressing for intracranial stimulation (ICS) across a range of intensities during and after drug administration, 20 adult male Sprague-Dawley rats were fixed with a chronically indwelling electrode for ICS of the lateral hypothalamus. Subsequently, rats pressed daily for four intensities of ICS, 2 min at each intensity. Subsequent to establishment of baseline pressing rates, rats were administered doses of amphetamine of 0, .5and/or 4mg/kg for 26 days. Opportunities to press for ICS were given .5and 23 h after injections. Following days of injections, there were further tests spanning 12 days. Initially, during the tests .5h after injections, the smaller dose of amphetamine slightly increased pressing over baseline and pressing of rats of 0mg/kg. Across days of injections the shift in pressing under the smaller dose was stable. Initially, the larger doses decreased pressing .5h after injections, however, across days of injections pressing increased to near baseline levels though never exceeding them. There were no discernible effects on pressing with tests 23 h after injections. Following the 26 day regimen of injections and testing, all press rates were at baseline levels. 11 references. (Author abstract)

003374 Deckard, Betty S.; Dalbeck, Robert; Jarvik, Lissy F. Veterans Administration Hospital, Brentwood, CA 94513 **Effect of morphine on response to pain: a twin study.** Behavior Genetics. 7(1):53-54, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, 10 pairs of male monozygotic twins were tested for their response to a painful stimulus (the cold pressor) three times on a morphine or placebo experimental day. Subjects' responses were measured before administration of the substance, 45 minutes after administration, and 4.25 hours after administration, taking measures on time elapsed until the subject reported pain, time elapsed until pain was perceived as intolerable, and the difference between reporting and stopping pain (pain sensitivity range, PSR). During both the drug and postdrug testing sessions, the average time required for stopping and the PSR scores were greater under the morphine condition than under the placebo condition. The ratio of the within twin pair to between twin pair variability revealed no significant twin factor on any measure, but there was a hierarchy of difference scores. It was concluded that morphine increases tolerance to a painful stimulus unrelated to a significant twin factor, although the mediation of effect by other genetic factors remains undetermined. (Author abstract modified)

003375 DiGiusto, E. L.; Bond, N. School of Behavioural Sciences, Macquarie University, North Ryde, New South Wales, 2113, Australia **Enhancement of pseudoconditioning and retardation of escape by low doses of ethanol.** Pharmacology Biochemistry and Behavior. 6(2):175-177, 1977.

Enhancement of pseudoconditioning and retardation of escape by low doses of ethanol was demonstrated in 80 mature male Wistar rats. Rats were injected with varying doses of ethanol or a saline control solution, then each animal was placed in a two compartment shuttlebox and given 25 trials during which footshock was presented every 60 seconds and tones were randomly programed. Shock escape latencies and frequencies of intercompartmental (pseudoconditioned) responses to the tone were measured. Results showed that 1 g/kg or 2 g/kg ethanol significantly retarded escape performance, but 2 g/kg ethanol significantly enhanced pseudoconditioning. Implications for the design of experiments concerned with the effects of drugs on learning processes, and for theories of the effects of ethanol on behavior, are suggested. 10 references. (Author abstract modified)

003376 Dixson, A. F.; Herbert, J. Wellcome Institute of Comparative Physiology, Zoological Society of London, Regent's Park, London N.W.1., England **Gonadal hormones and sexual behavior in groups of adult talapoin monkeys (Miopithecus talapoin).** Hormones and Behavior. 8(2):141-154, 1977.

The effect of gonadal hormones on sexual behavior in groups of adult talapoin monkeys was studied. Three heterosexual groups of six to eight monkeys were studied; all females were ovariectomized, whereas males were either intact or castrated. Aggressive hierarchies were evident in all groups, with females generally outranking males. When females were treated with estradiol, all males looked more frequently at the latters' sexual skin swellings, but only one male who was both dominant and intact copulated with them. Thus, either castration or low rank resulted in decreased levels of sexual behavior in male talapoins. The sexual behavior of dominant castrated males was restored by testosterone therapy, whereas subordinate castrates never copulated, even after large doses of testosterone, though penile erections and ejaculatory reflex (during masturbation) were restored. Following removal of a dominant male, the sexual behavior of the next male in rank was restored, provided he was not castrated and untreated. In contrast to males, female talapoins showed no consistent correlation between their rank and sexual activity. Estradiol therapy was without overall effect upon the frequency of female mounting behavior, though some females mounted and presented to one another more often. Estradiol treatment also caused females to present to males more frequently, but only to those that were sexually active (i.e.,who mounted females). 25 references. (Author abstract modified)

003377 Domino, K. B.; Domino, E. F. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109 **Effects of scopolamine and methscopolamine on acquisition and retention of rat one-way shuttle box behavior and total brain acetylcholine.** Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 224(2):248-257, 1977.

The effects of scopolamine HBr methscopolamine Br, and sodium Br (NaBr) on acquisition and retention of one way avoidance behavior and total brain acetylcholine (ACh) were studied in male albino rats. Compared to equimolar NaBr, scopolamine caused a dose related impairment in acquisition of avoidance responding while methscopolamine did not. Retention of avoidance behavior in trained rats was also disrupted, but the detrimental effect was smaller and occurred only following large doses of scopolamine. The percent escape behavior was not decreased by any of the treatments. It increased as avoidance was decreased. It is concluded that a muscarinic cholinergic antagonist with central actions like scopolamine affects selective aspects of avoidance behavior in low doses, and that these changes are highly correlated with brain ACh levels. 31 references. (Journal abstract)

003378 Domjan, Michael; Gregg, Barbara. Department of Psychology, University of Texas at Austin, Austin, TX 78712 **Long-delay backward taste-aversion conditioning with lithium.** Physiology & Behavior. 18(1):59-62, 1977.

In three experiments, rats were exposed to a 1.0% solution of sodium saccharin 60 min after the injection of 15ml/kg 0.12 lithium chloride to evaluate backward taste aversion conditioning. Rats learned an aversion to the saccharin flavor, as evidenced by the suppression of saccharin intake during a test session conducted several days later. This long delay backward taste aversion conditioning was not influenced by the duration of access to saccharin following the lithium injection. However, the effect was observed only with the 1.0% saccarin solution and not with a more dilute 0.1% solution. These findings demonstrate lithium induced backward taste aversion conditioning with a much longer unconditioned stimulus/conditioned stimulus interval than previously reported and suggest that the failure to observe conditioning with long drug taste intervals in certain situations may reflect ineffectiveness of the conditioning procedures used, rather than brevity of the aversive drug aftereffects. 16 references. (Author abstract modified)

003379 Duckrow, R. B.; Taub, A. Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510 **The effect of diphenylhydantoin on self-stimulation in rats produced by unilateral multiple dorsal rhizotomy.** Experimental Neurology. 54(1):33-41, 1977.

To investigate the hypothesis that self-mutilation of forelimbs in rats following multiple cervicothoracic dorsal rhizotomy may be dependent on the integrity of specific ascending spinal pathways, 30 female rats underwent multiple unilateral

cervicothoracic dorsal rhizotomy and were randomly assigned to treatment with 10, 15, 25, and 50mg/kg diphenylhydantoin intraperitoneally each day. Some animals received the drug vehicle alone as a control, and some animals were handled as the others but not treated. Videotape techniques were used to confirm and study the mutilation process, which appeared to be an aggressive rather than a passive one. Spinal cord histology was obtained. Diphenylhydantoin was shown to reduce the incidence of self-multilation from 89% (9 animals) to 40% (15 animals) when given at doses greater than 10mg/kg/day. The results support a possible etiologic role of central dysfunction and suggest that this process may involve hyperactive afferent pathways. 15 references. (Journal abstract)

003380 Dudek, Bruce C. State University of New York at Binghamton, Binghamton, NY 13901 **Acetaldehyde as a psychopharmacological agent: task specificity of genotypic differences.** Behavior Genetics. 7(1):56-57, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, the use of acetaldehyde as a pharmacological agent in a procedure designed to test its hypothesized role as the mediator of presumed conditioned taste aversion effects of alcohol in DBA/2 mice, but not in C57BL/6 mice, was reported. The two strains and their B6D2 F1 hybrid were used in a single pairing conditioned taste aversion paradigm where saccharin flavored water was the novel taste, and one of five doses of acetaldehyde was the poison. DBA/2 mice showed the most severe aversion when tested on 8 days of a two bottle, saccharin/water vs water preference test following the pairing of the novel taste with drug injection. C57BL/6 mice developed the least severe aversion, and the hybrids were intermediate at all doses. Administration of hypnotic doses in a sleep time test produced seemingly paradoxical results, with sleep time longest in the C57BL/6 and hybrid mice and shortest in the DBA/2 strain. Results are discussed from a perspective which views various behavioral determinations of alcohol sensitivity as indicators of diverse physiological responses to ethanol which may be under control of separate genetic systems. (Author abstract modified)

003381 Dykstra, Linda A.; Wharton, Walker; McMillan, D. E. Department of Psychology, University of North Carolina, Chapel Hill, NC 27514 **Antagonism of etonitazene's effects in rats and pigeons.** Pharmacology Biochemistry and Behavior. 6(2):215-219, 1977.

The effects of etonitazine, a potent narcotic with many effects similar to those of morphine, were studied in four pigeons under a multiple fixed-ratio, fixed-interval schedule of food presentation and in the rat under a continuous avoidance/escape schedule. A low dose of etonitazine increased rates of responding by pigeons under the fixed-interval component of the multiple schedule, whereas higher doses produced dose related decreases in responding under both components of the schedule. These effects were blocked by cyclazocine. Under the continuous avoidance/escape schedule, etonitazene produced only dose related decreases in rates of responding by rats, and these decreases were blocked by naloxene. A comparison of morphine and etonitazene is presented. 26 references. (Author abstract modified)

003382 Esposito, Ralph; Kornetsky, Conan. Laboratory of Behavioral Pharmacology, Division of Psychiatry, Boston University School of Medicine, Boston, MA 02118 **Morphine lowering of self-stimulation thresholds: lack of tolerance with long-term administration.** Science. 195(4274):189-191, 1977.

An experiment to investigate the lack of tolerance with long-term administration of morphine lowering of self-stimulation thresholds was undertaken. Rats were given increasing amounts of morphine over a period of weeks in order to achieve tolerance. Doses of the drug which initially reduced the threshold for self-stimulation behavior continued to do so after long-term administration. These results demonstrate a persistent central effect of morphine which may be related to the opiate "high." 16 references. (Author abstract modified)

003383 Fauquet, J. P.; Morel, E.; Demarty, C.; Rapin, J. R. Department de Pharmacologie, Centre de Recherches des Laboratoires Joullie, 20 bis, Quartier Boieldieu, La Defense, 92800 Puteaux, France **/Role of central catecholamines in the psychostimulant action of pyrovalerone./** Role des catecholamines centrales dans l'activite psychostimulante de la pyrovalerone. Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 224(2):325-337, 1977.

The role of central catecholamines in the psychostimulant action of pyrovalerone was studied. Comparison of the effects of alpha-methylpara-tyrosine (alpha-MPT) and/or reserpine pretreatment on mouse motor hyperactivity and rat stereotyped behavior induced by pyrovalerone and amphetamine suggest a different mechanism for these two substances. Both behavioral effects were abolished by alpha-MPT but were not altered by reserpine in the case of amphetamine, which presumably acts through a selective release of newly synthesized catecholamines from a functional pool. In contrast to this, pyrovalerone would increase spontaneous motor activity through a preferential release of norepinephrine from a storage pool since motor hyperactivity was not altered by alpha-MPT, especially during the first phase, whereas it was abolished by reserpine. Stereotyped behavior induced by pyrovalerone, was still present after pretreatment with alpha-MPT or reserpine; these data suggest action through release of both newly synthesized and stored dopamine. On the other hand, direct action on dopamine receptors might be involved after high doses of pyrovalerone and amphetamine since stereotyped behavior was found to be present after a combined pretreatment with alpha-MPT + reserpine. 39 references. (Journal abstract modified)

003384 File, Sandra E. Pharmacology Department, School of Pharmacy, University of London, London, England **Effects of N,N-dimethyltryptamine on behavioural habituation in the rat.** Pharmacology Biochemistry and Behavior. 6(2):163-168, 1977.

The effects of N,N-dimethyltryptamine (DMT) on habituation of exploration and distraction was studied in two experiments with 157 rats. Exploration was measured in a holeboard, and DMT (4mg/kg) greatly reduced the level of exploration, precluding any conclusions about the rate of habituation with this dose. However, 2mg/kg and 4mg/kg doses prevented the 24 hour retention of habituation of exploration. Habituation of distraction was measured by engaging rats in a baseline activity of licking and measuring distraction to tone stimuli by the interruption in licking. Doses of 2mg/kg and 4mg/kg DMT did not reduce the initial distraction to the tone stimulus, but the rate of habituation and its 24 hour retention were impaired. Mechanisms by which drugs may impair habituation are suggested. 15 references. (Author abstract modified)

003385 File, Sandra E. Pharmacology Department, School of Pharmacy, University of London, London, England **Effects of parachlorophenylalanine and amphetamine on habituation of exploration.** Pharmacology Biochemistry and Behavior. 6(2):151-156, 1977.

The effects of p-chlorophenylalanine (PCPA) and amphetamine on habituation of exploration behavior was studied in 49 rats with a holeboard apparatus. PCPA retarded the habituation of exploration in the rat over three successive days, but a more detailed analysis showed that this effect was not due to any retention deficit but was secondary to an impairment of habituation within each session. PCPA also disrupted the response of rats to a change of stimuli. Administration of 4mg/kg (+)amphetamine prevented exploration in the rat and a 2mg/kg dose reduced exploration and impaired within session habituation. In mice a dose of 1mg/kg impaired within sessions habituation without significantly reducing exploration. The nature of the deficits produced by the two drugs is discussed. 21 references. (Author abstract modified)

003386 Filho, N. G. Silveira; Graeff, F. G. Dept. of Pharmacology, Faculty of Medicine, 14.100 Ribeirao Preto, Sao Paulo, Brazil **Effect of tryptamine antagonists on self-stimulation: interaction with amphetamine.** Psychopharmacology (Berlin). 52(1):87-92, 1977.

Adult male rats were administered two tryptamine antagonists, cyproheptadine and methysergide, to investigate the role played by serotonergic (5-hydroxytryptamine; 5-HT) mechanisms in self-stimulation (SS) and the influence of these antagonists on the facilitatory effect of amphetamine. Rats with brain electrodes permanently implanted at the lateral hypothalamus and trained to lever press for response contingent brain electric stimulus presentation were used. Stimulus current was maintained at threshold level. Both tryptamine antagonists potentiated the enhancing effect of amphetamine on low SS rates, displacing to the left its dose effect curve. Cyproheptadine was at least three times more potent than methysergide. In addition, cyproheptadine, but not methysergide, caused dose related increased in SS rate when given alone. These results suggest that brain serotonergic systems play an inhibitory role in SS, opposing the facilitatory influence of adrenergic mechanisms. 50 references. (Author abstract modified)

003387 Gagliardi, Gregory; Thompson, Richard W. Department of Psychology, State University of New York, Albany, NY 12222 **Cholinergic blockade and tonic immobility in chickens.** Bulletin of the Psychonomic Society. 9(5):343-345, 1977.

To investigate the effects of cholinergic blockade on duration of tonic immobility (TI) and habituation to handling and the TI testing procedure, two groups of cockerel chicks (n=48) were tested following injection with scopolamine or saline. One week later half of each group was given a second test for TI following injection with saline or scopolamine. Results indicated that scopolamine significantly reduces the duration of TI and suggested some interference with the process of habituation, although the evidence for the latter was not conclusive. 5 references. (Author abstract)

003388 Gellert, Vance F.; Sparber, Sheldon B. Emory University, Department of Pharmacology, Atlanta, GA 30322 **A comparison of the effects of naloxone upon body weight loss and suppression of fixed-ratio operant behavior in morphine-dependent rats.** Journal of Pharmacology and Experimental Therapeutics. 201(1):44-54, 1977.

The effects of naloxone on fixed-ratio (FR)20 responding for food by drug naive rats, by rats pretreated with single, low doses of morphine and by rats implanted with morphine pellets were investigated. Administration of 10 or 25mg of naloxone (NX) per kg i.p. suppressed responding whereas 1mg of NX per kg was without effect. However, administration of 0.25mg of NX per kg to rats which had received 10 or 15mg of morphine sulfate per kg 48 hours previously induced small, but statistically reliable, decrements in responding. Rats implanted with one pellet containing 75mg of morphine base displayed tolerance to the depressant effects of the morphine pellet within 2 days after implantation. A systematic study of the effects of naloxone given to morphine tolerant dependent rats revealed good concordance between the amount of weight lost and the severity of behavioral disruption, within the same subject, after administration of the antagonist. Although 0.03mg of NX per kg given 3 to 6 days after pellet implantation significantly suppressed responding, 0.1mg of NX per kg was required to produce a significant reduction in bodyweight. Semiweekly injections of 1mg of NX per kg continued to suppress responding up to 4 weeks after implantation of a single morphine pellet. The bodyweight changes were significant only up to 3 weeks after implantation. The data suggest that disruption of fixed-ratio responding is a sensitive indicator of antagonist precipitated morphine withdrawal. 31 references. (Journal abstract modified)

003389 Gerald, Michael C.; Gupta, Tribhuwan K. Division of Pharmacology, College of Pharmacy, Ohio State University, Columbus, OH 43210. **Tolerance and cross-tolerance to the effects of amphetamine isomers on seizure susceptibility.** Journal of Pharmacy and Pharmacology (London). 29(2):115-116, 1977.

Tolerance and cross-tolerance to the effects of amphetamine isomers on seizure susceptibility was studied in mice. The animals were administered saline, (+)- or (-)-amphetamine once daily for six consecutive days. On the 7th day, a final dose of saline or amphetamine was injected 30 min before a constant intravenous infusion of leptazol. Thirty min after a single injection of (+)-amphetamine or (-)-amphetamine in mice pretreated with saline for 6 days, the leptazol seizure threshold was increased by 15 and 19 percent respectively. After chronic administration of each isomer, and injection of that isomer on day 7, tolerance was observed to the increase in seizure threshold; the dose of leptazol required to induce seizures in these animals was not significantly higher than that in mice chronically injected with saline. Cross-tolerance between the isomers was also demonstrated; chronic pretreatment with one isomer, and injection on the seventh day with its enantiomer, abolished the increase in seizure threshold normally elicited by a single injection of that isomer. The results suggest that while the amphetamine isomers increase seizure threshold by a common mechanism, a different neuronal interaction may be responsible for their proconvulsant effects. 10 references.

003390 Glick, Stanley D.; Cox, Russel D. Department of Pharmacology, Mount Sinai School of Medicine, CUNY, Fifth Ave. and 100th St., New York, NY 10029 **Changes in sensitivity to operant effects of dopaminergic and cholinergic agents following morphine withdrawal in rats.** European Journal of Pharmacology (Amsterdam). 42(3):303-306, 1977.

Changes in sensitivity to operant effects of dopaminergic and cholinergic agents following morphine withdrawal were studied in rats. Rats trained to bar press on either a fixed interval or fixed ratio schedule for water reinforcement were administered various doses of apomorphine, haloperidol, pilocarpine, and scopolamine both before and 1 to 4 months after a 3 day period of continuous morphine administration. All drugs monotonically depressed response rates on both schedules with increasing dose. Chronic morphine administration produced a persistent increase in sensitivity of apomorphine

and pilocarpine and a persistent decrease in sensitivity to haloperidol and scopolamine. The results suggest that both dopaminergic and cholinergic supersensitivity are likely to be involved in protracted abstinence phenomena. 17 references. (Author abstract modified)

003391 Goldberg, Steven R.; Tang, Andrew H. Laboratory of Psychobiology, Dept. of Psychiatry, Harvard Medical School, Boston, MA 02115 **Behavior maintained under second-order schedules of intravenous morphine injection in squirrel and rhesus monkeys.** Psychopharmacology (Berlin). 51(3):235-242, 1977.

Squirrel monkeys and rhesus monkeys were tested to determine whether they could be maintained under second order schedules of responding when morphine was injected intravenously only at the end of each session and each session was separated by at least a 23 hour interval. Every thirtieth keypressing reponse during a 60 minute interval produced a 2 second light; the first 30 response component completed after 60 minutes produced both the light and intravenous injection of morphine. A mean rate of approximately one response per second was maintained by doses of morphine ranging from 0.75mg/kg to 1.5mg/kg. A pause in responding after each light presentation was followed by rapid responding until the light was produced again; pauses became shorter as the 60 minute interval progressed. When brief light presentations were omitted, but morphine was still injected, response rates decreased and patterns of responding were altered. When saline injections were substituted for morphine, but the brief light was still presented, responding decreased markedly and patterns of responding were altered. 31 references. (Author abstract modified)

003392 Gonzalez, Fernando A.; Goldberg, Steven R. Yerkes Regional Primate Research Center, Emory University, Atlanta, GA 30322 **Effects of cocaine and d-amphetamine on behavior maintained under various schedules of food presentation in squirrel monkeys.** Journal of Pharmacology and Experimental Therapeutics. 201(1):33-43, 1977.

Dose response functions were determined for the effects of cocaine and d-amphetamine on lever pressing responses maintained under three schedules of food presentation: 1) a simple fixed-ratio schedule, 2) a multiple fixed-ratio, fixed-interval schedule and 3) a second order fixed-interval schedule with fixed-ratio components. These schedules generated a variety of rates and patterns of responding. The effects of the drugs on response rate depended on the control rates of responding. The highest overall rates of responding were maintained under the fixed-ratio schedule and under the fixed-ratio component of the multiple schedule. Both cocaine and d-amphetamine produced dose related decreases in these high response rates. Lower overall rates of responding were maintained under the second order schedule and under the fixed-interval component of the multiple schedule. Intermediate doses of cocaine or d-amphetamine (0.1to 1.0mg/kg) increased these lower rates of responding. Under the second order schedule and the multiple schedule, local response rates during successive segments of the fixed intervals were differentially affected by the drugs. Cocaine and d-amphetamine markedly increased low response rates that occurred during initial segments of the fixed intervals, but either had little effect on or decreased higher responses rates that occurred during later segments of the fixed intervals. Cocaine and d-amphetamine had similar qualitative and quantitative effects on responding, but d-amphetamine was longer lasting than cocaine. 7 references. (Journal abstract)

003393 Gordon, William C. State University of New York at Binghamton, Department of Psychology, Binghamton, NY 13901 **Susceptibility of a reactivated memory to the effects of strychnine: a time-dependent phenomenon.** Physiology & Behavior. 18(1):95-99, 1977.

Male albino rats were tested on an avoidance apparatus following intraperitoneal injection of strychnine sulfate to test the time dependency of susceptibility of a reactivated memory to CNS stimulation. It was demonstrated that the administration of strychnine following memory reactivation results in facilitated retention. Furthermore, this facilitation was shown to decrease as the interval between reactivation and the drug treatment was increased. The retrograde facilitation gradient was shown to have a much shorter duration than the gradient produced by injecting strychnine at various intervals after original learning. It was suggested that the reprocessing of reactivated information takes less time than the processing of new information. 20 references. (Author abstract modified)

003394 Gorelick, David A.; Bridger, Wagner H. Department of Psychiatry, Albert Einstein College of Medicine, Bronx, NY 10461 **Facilitation and disruption by mescaline and 3,4-dimethoxyphenylethylamine of shock avoidance in rats.** Psychopharmacology (Berlin). 52(2):157-163, 1977.

The effects of mescaline hydrochloride and its non hallucinogenic analogue 3,4-dimethoxyphenylethylamine hydrochloride (DMPEA) on shock avoidance in a shuttlebox were studied in male Long-Evans rats trained to high (above 88% good performers) or low (below 6% poor performers) stable base-line avoidance rates. In good performers, mescaline and DMPEA caused a dose dependent decrease in avoidance rate without affecting presession (5 min adaptation period) or intertrial shuttlebox crossings. In poor performers, mescaline caused a dose dependent increase in avoidance rate and intertrial crossings, without affecting presession crossings. The results suggest that mescaline, but not DMPEA, has dual facilitative and disruptive effects on avoidance behavior at similar dose ranges. The facilitative, but not the disruptive, effect may be related to changes in motor activity. 32 references. (Author abstract)

003395 Gotestam, K. Gunnar. Psychiatric Research Center, University of Uppsala, Ulleraker Hospital, Uppsala, Sweden **The discriminative properties of amphetamine analogues tested in self-administering rats under maintained stimulus control.** Addictive Behaviors. 2(1):27-33, 1977.

In a series of experiments, Sprague-Dawley rats trained to self-administer amphetamine were offered saline instead of amphetamine for self-administration during a 3 hr session to test the discriminative properties of amphetamine analogs. The self-administration behavior was then extinguished. When a noncontingent injection of d-amphetamine (0.25mg/kg), phenmetrazine (1.0or 2.0mg/kg), or diethylpropion (2.0mg/kg) was given prior to self-administration of saline, the response rate was elevated, and the extinction delayed, in contradistinction to experiments which started with a noncontingent injection of fenfluramine (.05mg/kg) or saline. When fenfluramine instead of saline was offered for self-administration, noncontingent preinjections of amphetamine also increased the response rate. The maintenance of stimulus control in rats self-administering amphetamine was studied by lever contingency shifts. After a mean of 2.27mg/kg of d-amphetamine, loss of stimulus control occurred, and the rats developed a high rate of responding on only one lever. It is concluded that in the doses employed phenmetrazine and diethylproprion have reinforcing properties, whereas fenfluramine has not. 20 references. (Author abstract)

003396 Green, A. R. MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE, England **Repeated chlorpromazine administration increases a behavioural response of rats to 5-hydroxytryptamine receptor stimulation.** British Journal of Pharmacology (London). 59(2):367-371, 1977.

The mechanism by which chronic administration of chlorpromazine enhances the hyperactivity syndrome produced in rats by administration of tranylcypromine and L-tryptophan was investigated. One injection of chlorpromazine did not enhance the hyperactivity response 24 hr later. The inhibition of the response observed after acute chlorpromazine injection also occurred if the tranylcypromine and L-tryptophan were administered 1 hr after the fourth daily dose of chlorpromazine. Administration of chlorpromazine for 4 da resulted in enhanced behavioral responses to the suggested 5-hydroxytryptamine (5-HT) agonist 5-methoxy-N,N-dimethyltryptamine on the fifth day. Chlorpromazine once daily for 4 da produced a slight increase in brain 5-HT concentration on day 5, but no difference in the rate of brain 5-HT synthesis or the rate of 5-HT accumulation after tranylcypromine and L-tryptophan administration. It is suggested that the enhanced behavioral response to 5-HT receptor stimulation following repeated chlorpromazine administration is the result of a blockade of 5-HT receptors. 17 references. (Author abstract modified)

003397 Guillemin, Roger; Ling, Nicholas; Burgus, Roger; Bloom, Floyd; Segal, David. Salk Institute for Biological Studies, La Jolla, CA 92037 **Characterization of the endorphins, novel hypothalamic and neurohypophysial peptides with opiate-like activity: evidence that they induce profound behavioral changes.** Psychoneuroendocrinology (Oxford). 2(1):59-62, 1977.

Endorphins, novel hypothalamic and neurohypophyseal peptides with opiate-like activity, were isolated and characterized from pig hypothalamus neurohypophysis, and their effects on behavior were studied. The primary structures of alpha-endorphin (AE), beta-endorphin (BE), and gamma-endorphin (GE) respectively were identical to those of beta-lipotropin subunits (61-76), (61-91), and (61-77). These peptides exhibited opiate-like activity in several assay systems. A series of analogs of the naturally occurring peptides was prepared and their biologic activities compared. Administration of synthetic AE, BE, or GE in the cisterna or through a cannula in the lateral ventricle in rats led to dramatic behavioral changes. AE produced minor analgesia, BE profound analgesia, and GE no analgesia. AE and BE lowered body temperature and GE elevated it. AE was a less potent tranquilizer than BE. All three endorphins produced "wet dog" shakes. GE regularly produced agitation and, in some animals, aggressive behavior. All effects of AE, BE, and GE were immediately reversed by naloxone. It was hypothesized that alterations in the homeostasis of the beta-lipotropin endorphin system may be causally involved in the mental diseases of man. 17 references.

003398 Ham, M. Ten. Laboratory of Pharmacology, National Institute of Public Health, P.O. Box 1, Bilthoven 2660, The Netherlands **Tolerance to the effects of delta9-THC on shuttlebox performance and body temperature.** Pharmacology Biochemistry and Behavior. 6(2):183-185, 1977.

Tolerance to the effects of delta9-tetrahydrocannabinol (THC) on shuttlebox performance and body temperature was studied in 32 rats. Two groups of subjects were trained in the shuttlebox and received THC either before or after being tested. The group receiving the drug before testing showed tolerance to the response inhibiting effect of THC within three to six sessions. The other group appeared also to be tolerant when they received THC before being tested. It is concluded that the tolerance to this effect probably is not learned, but has a physiological base, a hypothesis that is supported by the finding that during the same study all animals developed tolerance to the hypothermic effect of THC. 15 references. (Author abstract modified)

003399 Haranath, P. S. R. K.; Venkatakrishna-Bhatt, H. Department of Pharmacology, Kurnool Medical College, Kurnool A.P. 518 002, India **Sleep induced by drugs injected into the inferior horn of the lateral cerebral ventricle in dogs.** British Journal of Pharmacology (London). 59(2):231-236, 1977.

The effects of several cholinomimetic drugs, cholinolytic drugs, noradrenalin (NA) and 5-hydroxytryptamine (5-HT) on EEG and on behavior were studied in dogs after injection into the inferior horn of the left lateral cerebral ventricle and after injection into the body of the right lateral ventricle. Acetylcholine, physostigmine, pilocarpine, nicotine, atropine, hyoscine, tubocurarine, hexamethonium and NA all induced sleep after injection into the inferior horn but not after injection into the body of the lateral ventricle. The results with 5-HT were equivocal. The EEG recorded after tubocurarine showed high voltage slow waves during sleep and desynchronized activation during rapid eye movement sleep. It is suggested that the site for induction of sleep lies in structures lining the inferior horn of the lateral cerebral ventricle and that the cholinomimetic drugs probably act by a depolarizing block and the acetylcholine antagonists by a competitive block. 13 references. (Author abstract modified)

003400 Haycock, John W.; Van Buskirk, Roderick; Ryan, John R.; McGaugh, James L. Dept. of Psychobiology, School of Biological Sciences, Univ. of California, Irvine, CA 92717 **Enhancement of retention with centrally administered catecholamines.** Experimental Neurology. 54(2):199-208, 1977.

The effects of intracerebroventricular norepinephrine and dopamine on retention performance of mice were examined. The animals were trained in one of two inhibitory avoidance tasks and injected immediately posttraining with various doses of norepinephrine or dopamine. Retention was tested 24 hours later. In one training procedure, each mouse received a footshock as it stepped from one chamber to another in a "step-through" apparatus. In this task retention performance was enhanced by dopamine but not by norepinephrine. In the other training procedure, water deprived mice were first well trained to step from the first chamber into the second chamber and lick from a water spout. They were then given a footshock while licking. Norepinephrine, but not dopamine, enhanced retention of the lick avoidance training. These findings provide direct evidence that central catecholamines can modulate memory storage processes. 31 references. (Author abstract modified)

003401 Hayes, R. L.; Newlon, P. G.; Rosecrans, J. A.; Mayer, D. J. Neurobiology and Anesthesiology Branch, National Institute of Dental Research, NIH, Bethesda, MD 20014 **Reduction of stimulation-produced analgesia by lysergic acid diethylamide, a depressor of serotonergic neural activity.** Brain Research (Amsterdam). 122(2):367-372, 1977.

LSD was administered to adult male rats to investigate its influence on reduction of analgesia induced by electrical stimulation (SPA) of the dorsal raphe nucleus (DRN). Analgesia was assayed by a modified tail flick test. SPA dropped in the presence of LSD and returned to preLSD levels 48 hrs later. Administration of 2-brom-D-lysergic acid diethylamide

bitartrate (BOL) did not change SPA from values observed with saline controls. The results on SPA were consistent with the report that morphine analgesia (MA) is partially antagonized by comparable doses of LSD. It is hypothesized that the SPA antagonism of LSD is produced by inhibition of supraspinal serotonergic neurons, the activation of which is necessary for a complete manifestation of MA and SPA. It is suggested that the present results together with previous reports that interference with serotonergic function increases the sensitivity of rats to noxious stimuli warrant caution when administration of LSD is considered for humans experiencing chronic pain syndromes. 42 references.

003402 Hegmann, Joseph P.; Blakley, Ann. Department of Zoology, University of Iowa, Iowa City, IA 52240 **Neonatal androgen injection changes open-field behavior of mice.** Behavior Genetics. 7(1):23-27, 1977.

Open-field behavior of newborn female mice of the C57BL/6J and BALB/cJ inbred strains and their reciprocal F1 hybrids were studied after injection either with testosterone or with an oil medium alone. Both the repeatability and mean level of open-field activity scores over a 10 day test period increased in hormone injected animals compared with controls. Increased activity due to hormonal treatment was greater in hybrid females than in inbred females. There was no consistent effect of hormonal treatment on open-field defecation. Results suggest that the association between behaviors (consistent negative phenotypic correlation and strong negative genetic correlation) is not influenced by their common dependence on the hormone events of the estrus cycle. 11 references. (Author abstract modified)

003403 Hill, Shirley Y.; Mendelson, Wallace B.; Bernstein, David A. Department of Psychiatry, Washington University School of Medicine, 4940 Audubon Avenue, St. Louis, MO 63110 **Cocaine effects on sleep parameters in the rat.** Psychopharmacology (Berlin). 51(2):125-127, 1977.

Cocaine in 6mg/kg doses was administered orally and intraperitoneally to rats and sleep EEGs recorded in order to determine whether cocaine suppresses rapid eye movement (REM) sleep or other sleep parameters and to determine whether oral doses of the drug have a pharmacological effect in the dose range freely selected by laboratory animals. Cocaine significantly reduced total sleep time, slow wave sleep, and sleep latency. REM sleep was significantly suppressed during the first half of the sleep recording. These effects were evident by both routes of administration. The effects of cocaine on total sleep time in rats parallel those observed in humans. 16 references. (Author abstract modified)

003404 Hoffman, W. E.; Phillips, M. Ian. Neurobehavior Laboratory, Department of Physiology and Biophysics, University of Iowa, Iowa City, IA 52242 **Independent receptors for pressor and drinking responses to central injections of angiotensin II and carbachol.** Brain Research (Amsterdam). 124(2):305-315, 1977.

Effects of increased blood pressure and drinking behavior produced by angiotensin II and carbachol injection in rat brain ventricles were studied to determine whether these effects are produced by independent receptors or via a cholinergic circuit. A chronic rat preparation was used for recording blood pressure and drinking simultaneously during intraventricular injections of both drugs and intraventricular injections or intravenous infusions of appropriate antagonists. Results showed that drinking and blood pressure response to angiotensin II was blocked by P113, and was not blocked by atropine; carbachol effects were not blocked by P113, but were totally blocked by atropine. At high doses of atropine there was inhibition of both agents. The hormone and cholinomimetic administered together interacted, and both were inhbiited by adrenergic stimulation. It was concluded that angiotensin II and carbachol act upon independent receptors in the brain to produce blood pressure and drinking responses, but at some point they share common, central effector pathways. 32 references. (Author abstract modified)

003405 Hughes, R. N.; Syme, L. A.,; Syme, G. J. Dept. of Psychology, University of Canterbury, Christchurch 1, New Zealand **Open-field behaviour in sheep following treatment with the neuroleptics azaperone and acetylpromazine.** Psychopharmacology (Berlin). 52(1):107-109, 1977.

Adult female sheep (N=40) were administered the neuroleptics azaperone and acetylpromazine to investigate changes in open-field behavior. Azaperone significantly reduced the distance travelled, urination, and the time spent walking. However it increased nosing of the walls and floor (investigation). Azaperone also increased the numbers of sheep seen grazing and pawing and decreased the number heard vocalizing at least once. Acetylpromazine only reduced the number of sheep heard vocalizing. The main results were interpreted as supporting a superior reduction of emotional behavior by azaperone. It is suggested that, as with pigs, azaperone might be useful for treating sheep in stressful situations. 8 references. (Author abstract modified)

003406 Hutchinson, Ronald R.; Emley, Grace S.; Krasnegor, Norman A. Foundation for Behavioral Research, Augusta, ME 49012 **The effects of cocaine on the aggressive behavior of mice, pigeons and squirrel monkeys.** In: Ellinwood, E. H. (Ed.) Advances in behavioral biology. New York, Plenum Press, 1977. v. 21. (p. 457-480).

The effects of cocaine on the aggressive behavior of mice, pigeons, squirrels, and monkeys were investigated in five experiments. Experiment 1 studied the effects of acute and chronic cocaine administration on the dual baseline of postshock biting and preschock lever pressing for squirrel monkeys. The results indicate that at low dosages there is a differential increase in preschock behaviors and at the higher doses both behaviors decrease. Experiment 2 was designed to replicate in mice the effects of acute cocaine administration on a shock produced biting baseline. The results demonstrated that cocaine produced a decrease in biting attack by mice. Experiment 3 tested in the pigeon the influence of both acute and chronic administration of cocaine on the dual baseline of key pecks for food and postfood extinction attacks against a stuffed target pigeon. The results showed a decrease in attack responses. Experiment 4 tested drug influence upon biting attack performances by squirrel monkeys which were maintained by shock avoidance, while Experiment 5 tested the effects of cocaine upon a baseline of biting attack reinforced by the presentation of food on a variable interval schedule. The results indicate that aggressive behavior may be increased by cocaine administration in so far as an aggressive performance has certain features in common with other performances. It is concluded that cocaine does not show unique influences upon aggressive behavior and sometimes even decreases it. 13 references.

003407 Jacobs, Barry L.; Simon, Sanford M.; Ruimy, Daniel D.; Trulson, Michael E. Department of Psychology, Princeton University, Princeton, NJ 08540 **A quantitative rotational model for studing serotonergic function in the rat.** Brain Research (Amsterdam). 124(2):271-281, 1977.

The influence of serotonergic and catecholaminergic drugs on the induction of turning in rats with unilateral destruction of either central serotonergic or catecholaminergic nerve terminals was studied, suggesting a quantitative rotational model for studying serotonergic function in the rat. Unilateral injection of 5,7-dihydroxytryptamine into the medial forebrain bundle of rats produced serotonin depletions in the ipsilateral corpus striatum and ipsilateral forebrain. The animals showed a dose dependent increase in contralateral turning when pretreated with a peripheral decarboxylase inhibitor and then injected with L-5-hydroxytryptophan. Injections of parachloroamphetamine produced ipsilateral turning which could be blocked by prior serotonin depletion. Systemic administration of the catecholamine drugs L-DOPA, apomorphine, and d-amphetamine did not elicit consistent turning in either direction in the animals. Data indicated that the turning response of rats with unilateral destruction of brain serotonin nerve terminals provides a method for studying changes in serotonergic function, offering advantages of quantitative estimate of synaptic function and sensitivity of measurement of system activity. 29 references. (Author abstract modified)

003408 Jarbe, T. U. C.; Johansson, J. O. Department of Psychology, University of Uppsala, Box 227, S-751 04 Uppsala, Sweden **Pentobarbital, diazepam and bemegride: their effects on open-field behavior in the gerbil (Meriones unguiculatus).** Archives Internationales de Pharmacodynamie et de Therapy (Ghent). 225(1):88-97, 1977.

Open-field activity was measured in female mongolian gerbils treated with pentobarbital, or diazepam, either when given singly or in combination with the analeptic bemegride. The results indicated that the addition of bemegride normalized certain behaviors of the gerbils treated with pentobarbital and diazepam. The median effective doses of bemagride in incuding convulsion and death respectively were 12.0mg/kg and 22.5mg/kg. A mutual antagonism is apparent since no animal died after treatment with the drug combinations and seizure activity was also very much reduced. 24 references. (Author abstract)

003409 Jones, Barbara E.; Harper, Stanley T.; Halaris, Angelos E. Department of Psychiatry, University of Chicago, Chicago IL 60637 **Effects of locus coeruleus lesions upon cerebral monoamine content, sleep-wakefulness states and the response to amphetamine in the cat.** Brain Research (Amsterdam). 124(3):473-496, 1977.

The effects of locus coeruleus lesions on crebral monoamine content, wakefulness and paradoxical sleep, and response to amphetamine were studied in 16 cats. Radiofrequency lesions of the nucleus were performed in eight chronically implanted cats which were continuously recorded with an EEG. Three animals were administered amphetamine. Test results showed the majority of the locus coeruleus was bilaterally destroyed by the lesions which only minimally exceeded the boundaries of the nucleus within the dorsolateral pontine tegmentum. Noradrenaline was depleted noticeably in the paleocortex, neocortex, thalamus, and midbrain. EEG activation reappeared and represented a normal percentage of recording time on the third and subsequent days postlesion. The behavioral arousal and long-lasting EEG activation produced by amphetamine was qualitatively and quantitatively the same prelesion and postlesion. Despite alteration of certain components, paradoxical sleep reappeared within 48 hours and recovered to normal amounts by the second week postlesion. Muscle atonia was permanently absent in seven animals. Occipital piking was acutely redistributed across all sleep states and chronically reduced in frequency. Results indicate that the noradrenaline locus coeruleus neurons are not necessary for the tonic maintenance of EEG activity that occurs in normal wakefulness and in amphetamine produced arousal. Further, these neurons are not necessary for the occurrence of paradoxical sleep, although they may be involved in the modulation of occipital spiking. 69 references. (Author abstract modified)

003410 Kamioka, Toshiharu; Nakayama, Isao; Akiyama, Seigo; Takagi, Hiromu. Central Research Laboratories, Sankyo Co., Ltd., 2-58, 1-chome, Hiromachi, Shingawa-ku, Tokyo, Japan **Effects of oxazolam, cloxazolam, and CS-386, new anti-anxiety drugs, on socially induced suppression and aggression in pairs of monkeys.** Psychopharmacology (Berlin). 52(1):17-23, 1977.

The effects of several psychoactive drugs on socially induced suppressive behavior and aggressive behavior in pairs of monkeys were studied. These effects were examined both in instigator monkeys trained to lever press for food reinforcement and in attacker monkeys in whom aggressive behavior was induced by delivery of an electric shock concomitantly with each lever press of the instigator monkey. Benzodiazepine derivates, including the benzodiazepinooxazoles oxazolam, cloxazolam, and CS-386, at both ataxic and nonataxic doses, attenuated the socially induced suppression, but did not have an inhibitory effect on socially induced aggression. Chlorpromazine in both slightly sedative and nonsedative doses reduced neither socially induced suppression nor aggression. Imipramine did not produce any significant effect. It is concluded that some of the psychopharmacological properties of oxazolam, cloxazolam, and CS-386 resemble those of chlordiazepoxide and diazepam, but differ from those of of chlorpromazine or imipramine. 27 references. (Author abstract modified)

003411 Katz, R. J.; Carroll, B. J. Mental Health Research Institute, Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109 **Intracranial reward after Lilly 110140 (Fluoxetine HCl): evidence for an inhibitory role for serotonin.** Psychopharmacology (Berlin). 51(2):189-193, 1977.

The role of serotonin (5-HT) in self-stimulation was investigated by administration of the specific presynaptic 5-HT reuptake inhibitor fluoxetine hydrochloride (Lilly 110140) to rats trained to bar press for rewarding stimulation to the caudal portion of the medial forebrain bundle. Rates of self-stimulation were reduced in proportion to drug dosage, and these reductions were partially reversed by methysergide. The findings are consistent with previous reports suggesting an inhibitory role for 5-HT in self-stimulation. 46 references. (Author abstract modified)

003412 Klein, Stephen B.; Mikulka, Peter J.; Domato, Gary C.; Hallstead, Carol. Old Dominion University, Norfolk, VA 23508 **Retention of internal experiences in juvenile and adult rats.** Physiological Psychology. 5(1):63-66, 1977.

To test retention of internal experiences, an equal number of adult and juvenile female Sprague-Dawley rats (n, 14) received one of four treatments during Phase 1 of the study. Phase 1 consisted of four sucrose saline pairings (S), four illness experiences (I), four sucrose illness pairings (SI), or four saline injections (C). After the last Phase 1 treatment, all subjects received a 30 min exposure to sucrose and water followed by a lithium chloride injection during the second phase of the experiment. Phase 2 began either 1 or 28 days following the last injection. Each subject continued to receive sucrose illness until a suppression criterion was reached for a max-

imum of 4 test days. Adult and juvenile animals that had received sucrose illness pairings in Phase 1 and tested 1 or 28 days later drank significantly less sucrose than their appropriate control animals. The I treatment adult and juvenile rats at the 1 day retention interval developed the taste aversion more slowly than control animals. Furthermore, the adult, but not the juvenile, rats given sucrose exposures prior to conditioning drank more sucrose than their control rats on day 2 of training at both intervals. At the 28 day retention test, suppression of sucrose intake was equivalent in adult and juvenile rats in I and C animals. It was concluded that young and adult animals can recall prior taste aversion experiences over a 28 day interval but apparently do not remember illness alone experiences 28 days later. 13 references. (Author abstract)

003413 Kokkinidis, Larry; Anisman, Hymie. Department of Psychology, Carleton University, Ottawa, Ontario K1S 5B6, Canada **Perseveration and rotational behavior elicited by d-amphetamine in a Y-maze exploratory task: differential effects of intraperitoneal and unilateral intraventricular administration.** Psychopharmacology (Berlin). 52(2):123-128, 1977.

The differential effects on intraperitoneal (i.p.)and unilateral intraventricular (i.vt.)administration on perseveration and rotational behavior elicited by d-amphetamine (AP) in a Y-maze exploratory task were studied in mice. Both routes of injection produced circling behavior in a dose related fashion when animals were tested in a circular alleyway. In a free running Y-maze alternation task, i.p. injection induced perseveration (i.e. animals consecutively visited only 2 arms of the maze), but i.vt. injection augmented alternation behavior normally seen in saline treated mice. It was suggested that Y-maze performance following i.vt. AP reflects response perseverations, whereas systemic AP produced stimulus perseveration (repetition of location rather than direction). Moreover AP induced circling produced by i.p. administration probably is an artifact of drug induced stimulus perseveration as opposed to motor biases observed following i.vt. injections. 21 references. (Author abstract modified)

003414 Korczyn, Amos D. Department of Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel **Combined use of neuroleptic drugs.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 179-184).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center in Ezrath Nashim in Jerusalem, Israel, in December 1975, the practice of treating patients with combinations of neuroleptic drugs is discussed, and studies of the effects of various antipsychotic drugs, alone and in combination, on spontaneous activity and on amphetamine induced hyperactivity in mice are reported. It is posited that clinical studies do not support the idea that combinations of neuroleptic drugs are more effective in patients than are single drugs. Animal studies have revealed that: 1) chlorpromazine and haloperidol, which affect the same receptors, have additive effects on spontaneous activity and amphetamine induced hyperactivity in mice; 2) pretreatment with reserpine markedly potentiates the chlorpromazine induced reduction of spontaneous activity and amphetamine induced hyperactivity in mice; and 3) promethazine, a nonantipsychotic phenothiazine derivative, antagonizes the effects of haloperidol on spontaneous activity and amphetamine induced hyperactivity in mice. It is suggested that the combined use of antipsychotic drugs can be studied in experimental animals and that combinations of drugs which have different mechanisms of action should be studied. 6 references.

003415 Kovacs, Gabor L.; Telegdy, Gyula; Lissak, Kalman. Department of Physiology, University Medical School, Pecs, Hungary **Dose-dependent action of corticosteroids on brain serotonin content and passive avoidance behavior.** Hormones and Behavior. 8(2):155-165, 1977.

The affect of dependent action of corticosteroids on brain serotonin content on passive avoidance behavior in rats was studied. Corticosterone, 1.0and 5.0mg/kg, improved passive avoidance behavior based on fear versus thirst conflict situation. Corticosterone, 1.0mg/kg, increased the serotonin (5-HT) content in the hypothalamus and mesencephalon; 5.0mg/kg of corticosterone had no effect. Plasma corticosterone level increased in a dose dependent manner after corticosterone treatment. DL-Parachlorophenylalanine (PCPA) impaired passive avoidance behavior and decreased the hypothalamic and mesencephalic 5-HT level. After PCPA treatment, the plasma corticosterone level was slightly increased. PCPA pretreatment was able to prevent the action of 1.0and 5.0mg/kg of corticosterone on behavior as well as on brain 5-HT level. Corticosterone, 10.0mg/kg, impaired passive avoidance behavior, decreased the hypothalamic and mesencephalic 5-HT content, and increased the plasma corticosterone level. Monoamine oxidase inhibitor (nialamide) treatment improved the passive avoidance behavior and increased the 5-HT level in the hypothalamus and mesencephalon. The plasma corticosterone level did not change significantly. Nialamide pretreatment abolished the behavioral action of 10.0mg/kg of corticosterone as well as its action on brain 5-HT level. A large dose of corticosterone (25.0mg/kg) and 2.5mg/kg of 6-dehydro-16-methylenhydrocortisone (6DH) had a similar action on passive avoidance behavior and on brain serotonin level as 10.0mg/kg of corticosterone; however, the plasma corticosterone level was increased only in corticosterone treated animals and was significantly decreased after 6DH. 11-Deoxycorticosterone (DOC) was ineffective on passive avoidance behavior and on brain serotonin content, whereas it slightly decreased the plasma corticosterone level. Data suggest that the corticosterone has dose dependent dual action on passive avoidance behavior, and its action is, at least partly, mediated via changed brain serotonin metabolism. The action seems to be a glucocorticoid specific one since mineralocorticoid (DOC) is ineffective on this behavioral pattern. 20 references. (Author abstract modified)

003416 Kuribara, Hisashi; Higuchi, Yoichiro; Tadokoro, Sakutaro. Behavior Research Institute, Gunma University, Maebashi 371, Japan **Effects of central depressants on rota-rod and traction performance in mice.** Japanese Journal of Pharmacology (Kyoto). 27(1):117-126, 1977.

To study the effects of the central depressants, chlorpromazine, diazepam, pentobarbital, and ethanol on rota rod and traction performances in mice, the walking technique of the animals on the rotating rod (3 cm in diameter, 24 r.p.m.)was well established after about 15 trials, and was maintained for one week thereafter. No training was required for the traction. Both the rota rod and traction performances were inhibited by chlorpromazine, diazepam, pentobarbital and ethanol in parallel with the dosages. However, the sensitivities to one same drug markedly differed between the two performances. Chlorpromazine more than diazepam inhibited the rota rod, while in the traction performance the inhibition with diazepam was greater than that with chlorpromazine. Pentobarbital and ethanol inhibited the two performances to nearly the same degree. On the basis of the present results, the rota rod test is considered to be suitable for the estimation of the positive adaptability to forced motor activity, and the

traction for that of muscle relaxation. It was concluded that by comparing the dose effect relationships in the two performances, it may be possible to elucidate the characteristics of various central depressants, and to apply these procedures for the screening test in drug evaluations. 17 references. (Author abstract)

003417 Kurtz, Perry; Palfai, Tibor. Toxicology Division, U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, Aberdeen, MD **Effects of reserpine on retention of escape reversal in mice: absence of state-dependent learning.** Journal of Comparative and Physiological Psychology. 91(2):393-406, 1977.

A discriminated escape training paradigm was used to study the effects of reserpine on learning and memory in mice. Intraperitoneal injection of reserpine before reversal training had no effect on acquisition but did produce a time and dose dependent impairment of retention test performance 10 days later. These results suggested that reserpine may have interfered with some aspect of memory storage. Retention impairments observed when a 2.0mg/kg reserpine injection was given 2 hr before reversal training were not attenuated by readministering the drug before testing, a finding that provides no support for a state dependency interpretation. Furthermore, animals treated with reserpine exhibited inferior retention of previous training, regardless of the pharmacological state present during that learning. This was interpreted as a drug induced impairment of memory retrieval. In addition, performance during the initial discriminated escape training session suggested that reserpine may also impair acquisition under some conditions. The results are discussed in terms of the possible roles of biogenic amines in arousal, learning, and memory. 38 references. (Author abstract)

003418 Lanier, Linda Patia; Isaacson, Robert L. Department of Psychology, State University of New York, Binghamton, NY 13901 **Early developmental changes in the locomotor response to amphetamine and their relation to hippocampal function.** Brain Research (Amsterdam). 126(3):567-575, 1977.

Early developmental changes in the locomotor response to amphetamine and their relation to hippocampal function in rats are examined. Results suggested a curvilinear sensitivity to DL-amphetamine with age as measured by locomotion in an open field. Rats tested between 18 and 22 days postnatally showed a significant increase in activity after all doses. On postnatal days 34 to 38, rats were unresponsive to any of the doses. The adult pattern -- an increase in activity after 2 and 5mg/kg and either no increase or a reduction in activity after 10mg/kg -- was seen in rats that began testing on postnatal day 45. In rats tested between 45 and 49 days of age and in adulthood, the highest dose produced a significant decrease in activity when compared with the other groups. However, rats tested beginning on postnatal day 18 showed an increase in activity at the highest dose. It is suggested that reasons for this changing pattern lie in interactions among brain systems that are maturing at different rates, a suggestion that is supported in a second experiment showing differential responses to amphetamine by rats of various ages with hippocampal damage. 15 references. (Author abstract modified)

003419 Lanoir, J.; Lardennois, D. Laboratoire de Neurophysiologie, C. N. R. S., 31 Chemin Joseph-Aiguier, 13274 Marseille Cedex 2, France **The action of lithium carbonate on the sleepwalking cycle in the cat.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(5):676-690, 1977.

To determine if lithium carbonate would modify EEG appearances in the cat, and to investigate the possible effects of lithium on the sleepwalking cycle, polygraphic recording from three adult cats was carried out during 24 hour periods before, and on different days after, beginning treatment with lithium carbonate. With low doses important morphological changes were observed 5 days later while a new balance of the sleepwalking stages occurred. The EEG of each stage was characterized by slowing and amplitude increase of the different frequencies. The rhythms which appeared in long runs during quiet wakefulness and paradoxical sleep (PS) in the somaethetic cortex (mu rhythm) and the visual areas (alpha rhythm) were increased, slowed and almost continuously present. The percentage of time of deep slow wave sleep (DSWS) was increased from 38% to 55%. Conversely, the waking and PS times were both reduced, the latter from 18% to 10%. In contrast with human data, the mean duration of PS episodes was unchanged. Furthermore, lithium induced a slight dissociation between EEG activity and waking behavior. With toxic dose all the above changes were again observed, but more conspicuously. During wakefulness and SWS, bursts of generalized paroxysmal events appeared, in frequent association with a myoclonic jerk. SP became atypical and its percentage of time was drastically reduced. 68 references. (Author abstract)

003420 Lassen, Jorgen Buus. Department of Pharmacology, A/S Ferrosan, Sydmarken 5, DK-2860 Soborg, Denmark **Inhibition of apomorphine-induced hypermotility in rats by chlorpromazine, perphenazine, thioridazine and melperone.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(3):418-429, 1977.

The inhibition of apomorphine (APO) induced hypermotility in rats by chlorpromazine (CZ), perphenazine (PZ), thioridazine (TZ), and melperone (MP) was studied. Administration of the neuroleptics 30 min before APO inhibited APO induced hypermotility. When the dose of APO was increased, higher doses of the neuroleptics were required to inhibit the hypermotility. By varying the dose of CZ, TZ, and MP, partial APO antagonism was found, but increase of the PZ dose resulted in complete APO inhibition. Hypermotility produced by APO is presumably dependent on direct stimulation of dopamine receptors. Neuroleptics blocking some, but not all, dopamine receptors may cause no, or weak, parkinsonian side effects. 59 references. (Author abstract modified)

003421 Lucas, L. A.; Scott, J. P. Bowling Green State University, Bowling Green, OH 43402 **Hyperactivity in two dog breeds and their hybrids.** Behavior Genetics. 7(1):74-75, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, inhibitory (restraint) training in two breeds of dogs (beagle and Telomian) and their reciprocal F1 generations was used to investigate genotypic differences in hyperactivity and its response to the stimulant d-amphetamine sulfate and to develop a model for hyperactivity in children. The restraint training task required the puppy at 8 weeks and at 16 weeks to stay for 60 seconds on a 40 inch square board placed in its home room, with restraint by a choke collar and lead if it did not. Effects of three doses of d-amphetamine sulfate on board time were measured, yielding data from one litter in each genotype. Results were that beagles and F1 hybrid puppies showed the paradoxical effect (more time on board) with the drug, but not Telomians; more puppies showing the paradoxical effect were found in the F1 litter of a Telomian mother than those with a beagle mother; and puppies showing the paradoxical effect were found among

those classified as both normal and hyperactive. It was suggested that a maternal effect may be present and that hyperactivity and nature of the response to d-amphetamine sulfate may be dissociated characters. (Author abstract modified)

003422 Lynch, James J.; Fertziger, Allen P. Department of Psychiatry, Institute of Psychiatry and Human Behavior, University of Maryland School of Medicine, Baltimore, MD 21201 **Drug addiction: light at the end of the tunnel?** Journal of Nervous and Mental Disease. 164(4):229-230, 1977.

Reference is made to the recent biochemical discovery that the body is capable of producing endogenous analgesic substances and to the implications of this discovery for the therapeutic treatment of drug addiction. This finding shed some light on earlier experiments in which dogs previously conditioned to morphine were placed on an extinction program. After periods of 3 months of extinction trials, a single injection of the narcotic antagonist naloxone was administered at the end of the conditional stimulus. Almost immediately withdrawal behavior became evident. It is suggested that the production of endogenous analgesic substances in the brain is highly resistant to extinction, and hence addictive. On the basis of this speculation hope is expressed that the link between endogenous substances and Pavlovian conditioning will be translated into clinical utility in the very near future. 6 references.

003423 MacLean, Keith I.; Littleton, John M. Glaxo Research Ltd., Greenford, Middlesex UB6 OHE, England **Environmental stress as a factor in the response of rat brain catecholamine metabolism to delta8-tetrahydrocannabinol.** European Journal of Pharmacology (Amsterdam). 41(2):171-182, 1977.

In rats housed normally (aggregated, food and water ad lib) for 14 days delta8-tetrahydrocannabinol (THC) produced mild sedation and minimal hypothermia. An increase in noradrenaline synthesis was observed, but brain dopamine metabolism was unchanged. In rats removed from this normal environment to conditions of isolation and food deprivation for 24 hours, THC produced immobility, marked hyperreactivity, and hypothermia. Brain noradrenaline metabolism was found to be unchanged by THC under these conditions, but significant changes in striatal dopamine metabolism were observed. The changes are consistent with increased dopamine reuptake in striatum produced by this combination of THC and novel environment. It is suggested that some of the behavioral effects of cannabis administered under stressful conditions may be related to alterations in striatal dopamine metabolism. 32 references. (Author abstract modified)

003424 Manning, Frederick J.; Jackson, Mason C., Jr. Walter Reed Army Institute of Research, Washington, DC 20012 **Enduring effects of morphine pellets revealed by conditioned taste aversion.** Psychopharmacology (Berlin). 51(3):279-283, 1977.

A conditioned taste aversion assessment technique to determine the enduring effects of morphine pellets, which is more sensitive than any technique currently in use, is outlined. Morphine pellets (75mg) were implanted subcutaneously in 50 albino rats. Three days later, following 24 hours without water, these rats were given access to a saccharin solution for 30 minutes, then injected with naloxone hydrochloride. The classical abstinence signs were noted in these subjects but not in the controls. When given an opportunity to drink either saccharine solution or water 24 hours later, the experimental rats drank significantly less saccharin than any of the control groups. Similar drinking patterns were found even when naloxone injection was delayed as long as 3 weeks after pellet injection, when none of the classical abstinence signs were seen and serum levels of morphine and its metabolites were 100 time lower according to radioimmunoassay. This simple and objective technique is thus more sensitive as a measure of prior morphine exposure than any of the commonly used indices. The continued utility of a dependent/nondependent dichotomy is examined. 18 references. (Author abstract modified)

003425 Marshall, John F.; Ungerstedt, Urban. Departments of Psychobiology and Psychiatry, Univeristy of Pittsburgh, Pittsburgh, PA 15260 **Supersensitivity to apomorphine following destruction of the ascending dopamine neurones: quantification using the rotational model.** European Journal of Pharmacology (Amsterdam). 41(4):361-367, 1977.

A new surgical preparation useful in the quantification of the degree of supersensitivity to dopamine (DA) receptor stimulants using the rotational model is described. One group of rats received a unilateral injection of 6-hydroxydopamine (6-OHDA), which destroys the DA containing neurones in one hemisphere, followed by a diencephalic electrocoagulation which interrupts both afferents and efferents of the striatopallidal complex in the opposite hemisphere. Another group of animals received only the unilateral electrocoagulation. When given apomorphine both groups rotated toward the side of the electrocoagulation; however, the 6-OHDA treated animals were 10 to 40 times more sensitive to the effects of apomorphine. The results contrast with previous reports in which behavioral sensitivity to apomorphine was increased twofold to sevenfold following partial degeneration of central DA neurones or following the chronic administration of DA synthesis inhibitors or DA receptor blocking agents. The extent of loss of DA appears to be a critical factor in determining the degree of supersensitivity which develops. 27 references. (Author abstract modified)

003426 Martin, B. R.; Dewey, W. L.; Aceto, M. D.; Adams, M. D.; Earnhardt, J. T.; Carney, J. M. Department of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298 **A potent antinociceptive cannabinoid which lacks opiate substitution properties in monkeys.** Research Communications in Chemical Pathology and Pharmacology. 16(1):187-190, 1977.

The activity of (-)-9-nor-9beta-hydroxy-hexahydrocannabinol ((-)-9-nor-9beta-OH-HHC) in the mouse tail flick and the p-phenylquinone (PPQ) abdominal stretching tests, in the single dose suppression test (SDS) in rhesus monkeys, and in cardiovascular properties of the alpha and beta isomers of 9-nor-9-OH-HHC in anesthetized dogs was investigated as an extension of studies predicting analgesic activity of these drugs in humans. (-)-9-nor-9beta-OH-HHC produced hypotension and bradycardia in dogs, was a potent antinociceptive agent in the mouse tail flick and PPG abdominal stretching tests, but did not reverse the effects of morphine withdrawal in dependent monkeys. It was not established whether (-)-9-nor-9beta-OH-HHC will produce physical dependence on chronic administration to animals. 5 references. (Author abstract modified)

003427 Matsui, Y.; Deguchi, T. Central Research Laboratories, Sankyo Co. Ltd., Hiromachi 1-chome Shinagawaku, Tokyo 140, Japan **Cataleptic action of nitrazepam and brain dopamine function in mice.** Neuropharmacology. 16(4):253-258, 1977.

The cataleptic action of nitrazepam and brain dopamine (DA) functions were studied in mice. Impairment of the righting reflex elicited by nitrazepmam was markedly poten-

tiated by pretreatment with reserpine, alpha-methyl-p-tyrosine (AMT), haloperidol, and chlorpromazine, but not by bis(4-methyl-1-homopiperazinylthiocarbohyl)disulfide (FLA-63) or p-chlorphenylalanine (CPA). The pretreatments which potentiated the nitrazepam action were much less active in potentiating the action of phenobarbital on the reflex. The state produced by small doses of nitrazepam in combination with the former drugs was different from that produced by large doses of nitrazepam or phenobarbital and was considered to be catalepsy rather than the loss of righting reflex. The greater the depletion of brain DA after injection of reserpine, the more potentiated was the action of nitrazepam in causing catalepsy-like behavior. AMT decreased brain noradrenaline (NA) and DA, but increased brain serotonin (5-HT). Reserpine also decreased NA and 5-HT; FLA-63 decreased NA but had no effect on DA or 5-HT, while CPA decreased 5-HT selectively. Cataleptic action of small doses of nitrazepam induced after AMT disappeared with administration of L-dihydroxyphenylalanine and L-alpha-hydrazino-alpha-methyl-beta-(3,4-dihydroxyphenyl)-propionic acid monohydrate (MK-486), but that after reserpine was not influenced with the same treatment. The findings suggest that an impairment of the DA system facilitates the cataleptic action of small doses of nitrazepam. 22 references. (Author abstract modified)

003428 McCaughran, James A., Jr.; Corcoran, Michael E. Department of Psychiatry, University of British columbia, Vancouver, B.C. V6T 1W5, Canada **Lithium reduces preference for ethanol induced by hypothalamic stimulation.** Journal of Pharmacy and Pharmacology (London). 29(2):120-121, 1977.

The effects of lithium on the chronic preference for concentrated solutions of ethanol established by hypothalamic stimulation was investigated in rats to determine whether lithium could reduce the consumption of ethanol by organisms with a history of persistent self-administration. For the first 30 days of the experiments 10 of the rats received 30 min of daily hypothalamic stimulation. On day 31 stimulation was discontinued and the ethanol intake of the rats was examined until day 170. Beginning on day 171, a day in which only water was available, the rats received twice daily injections of lithium chloride. After 10 days (5 days of ethanol presentation) the dosage of lithium was raised and administered for 6 additional days (3 ethanol days). A control group of rats prepared in the same manner received injections of saline instead. At the time injections of lithium began, 10 of 10 rats subjected to hypothalamic stimulation had developed a consistent preference for ethanol, whereas 4 of 8 nonstimulated rats preferred ethanol to water. Administration of lithium produced a significant reduction in intake of ethanol. The reduction in ethanol intake was evident with the lower dosage of lithium but the subsequent doubling of the dosage of lithium failed to produce a further reduction. These results seem to confirm that parenteral treatment with lithium reduces the oral intake of ethanol in rats, and that cessation of treatment with lithium is followed by a rapid recovery of intake to pretreatment levels. The value of lithium as a therapeutic agent for clinically treating chronic alcoholism may require further investigation. 7 references.

003429 Meyerson, Bengt J.; Terenius, Lars. Department of Medical Pharmacology, University of Uppsala, Box 573, Biomedicum, S-75123 Uppsala, Sweden **Beta-endorphin and male sexual behavior.** European Journal of Pharmacology (Amsterdam). 42(2):191-192, 1977.

The effects of beta-endorphin (BE) on copulatory behavior were studied in male rats. Exploratory activity in an observation cage was not influenced by 1 microgram BE but slightly reduced by 3 micrograms. Scores for sociosexual approach towards a castrated male were not affected by BE. The 1 microgram BE treated males investigated the anogenital area of an estrous female very actively and pursued her; however, only 5/13 males initiated mounting (statistically different from controls.)Those males who initiated mounting had a longer latency and a low mount frequency compared to controls. There was no evidence of muscular rigidity or signs of a cataleptoid state at the lower dose level; on the contrary, the animals were very active. After 3 micrograms BE, the frequency of pursuit decreased and after 30 micrograms, a cataleptoid state was evident. The results strengthen the hypothesis that changes in beta-lipotropin-endorphin homeostasis can cause profound behavioral changes. 3 references.

003430 Mills, Kenneth C.; Bean, J. William; Hutcheson, J. Stanford. Center for Alcohol Studies and Department of Psychiatry, University of North Carolina, Division of Health Sciences, Chapel Hill, NC 27514 **Shock induced ethanol consumption in rats.** Pharmacology Biochemistry and Behavior. 6(1):107-115, 1977.

The temporal and volumetric changes in ethanol consumption by rats exposed to recurring schedules of inescapable random shock were investigated. The animals in Experiment 1, which had a choice between ethanol and water, increased their voluntary ethanol consumption immediately after the shock schedule. The postshock changes occurred with both 5% and 10% V/V ethanol, were specific to the presence of shock and were not reflected by measures of total daily ethanol intake. Experiment 2 exposed rats to extended 22 hr stress sessions, during which each animal had four simultaneous fluid choices available: water, saccharin 0.1% W/V, ethanol 5% V/V, and ethanol 10% V/V. Temporal intake patterns for both 5% and 10% ethanol showed pronounced peaks for the interval immediately following the shock schedule. A shift of intake from 5% to 10% ethanol was also demonstrated with increasing time under shock, while saccharin and water intake decreased. The results are interpreted as a relationship between voluntary ethanol intake and escape from the consequences of stress. 37 references. (Journal abstract modified)

003431 Moja, Egidio A.; Stoff, David M.; Gillin, J. Christian; Wyatt, Richard Jed. Laboratory of Clinical Psychopharmacology, Division of Special Mental Health Research, NIMH, St. Elizabeths Hospital, Washington, DC 20032 **Beta-phenylethylamine and animal behavior. (Unpublished paper).** Rockville, MD, NIMH, 1977. 38 p.

A series of studies were undertaken to investigate the effects of beta-phenylethylamine (PEA) on the behavior of animals. In a general way, PEA induces "amphetamine-like" behavioral effects in animals. The possible role of PEA in mental illness is discussed. The data reveal that PEA induces unusual behavioral effects in animals, that no tolerance has been reported to these effects, and that drugs like neuroleptics, which are efficacious in the treatment of mental illnesses, can block these effects. These findings can only further interest in this compound. PEA is one of the few endogenous compounds which produce recognizable behavioral abnormalities immediately after exogenous administration. 65 references.

003432 Mora, F.; Myers, R. D.; Sanguinetti, A. M. Departments of Psychological and Biological Sciences, Purdue University, Lafayette, IN 47907 **Self-stimulation of the MFB or VTA after microinjection of haloperidol into the prefrontal cortex of the rat.** Pharmacology Biochemistry and Behavior. 6(2):239-241, 1977.

The effect of haloperidol, a dopamine receptor antagonist, on self-stimulation of the medial forebrain bundle (MFB) or the ventral tegmental area (VTA) was studied after microinjection into the prefrontal cortex of six rats. It was found that injections failed to attenuate self-stimulation in either structure. However, when haloperidol was injected into the caudate/putamen complex, a decrease in self-stimulation occurred in these structures. Results suggest that dopamine in the medial prefontal cortex is not necessarily a part of the neurochemical substrate underlying self-stimulation of the VTA or MFB. 19 references. (Author abstract)

003433 Morgan, John M.; Routtenberg, Aryeh. Cresap Neuroscience Laboratory, Northwestern University, Evanston, IL 60201 **Angiotensin injected into the neostriatum after learning disrupts retention performance.** Science. 196(4285):87-89, 1977.

The effects of angiotensin II, a peptide endogenous to the nigro-neostriatal system, were studied relative to the possible role of that system in memory mechanisms. Angiotensin II, injected into the dorsal neostriatum of rats 5 minutes after they had learned a passive avoidance task, disrupted the retention of the task 24 hours later. Identical neostriatal injections given 22 hours after learning (2 hours before retention) were without effect on retention performance. Ventral neostriatum or posterior thalamus were ineffective sites for injection of angiotensin. Injection of thyrotropin releasing hormone or lysine-8-vasopressin into the dorsal neostriatum was ineffective. These findings indicate a possible role for endogenous angiotensin in the neostriatum on retention performance and suggest potential involvement in mnemonic processes. 33 references. (Author abstract modified)

003434 Morihisa, John M.; Glick, Stanley D. Mount Sinai School of Medicine, City University of New York, New York, NY 10029 **Morphine-induced rotation (circling behavior) in rats and mice: species differences, persistence of withdrawal-induced rotation and antagonism by naloxone.** Brain Research (Amsterdam). 123(1):180-187, 1977.

The existence of morphine induced rotation, withdrawal induced rotation, and the effects of naloxone in rats and mice were investigated. In both species morphine induced rotation and the cessation of chronic morphine administration induced rotation. Both rotations were associated with a neurochemical change in the striatum and were blocked by naloxone. It is concluded that this indicates that an endogenous morphine-like substance persists long after morphine itself is eliminated. 27 references.

003435 Mukherjee, B. P.; Bailey, P. T.; Pradhan, S. N. Department of Pharmacology, Howard University, College of Medicine, Washington, DC 20059 **Correlation of lithium effects on motor activity with its brain concentrations in rats.** Neuropharmacology. 16(4):241-244, 1977.

The correlation of lithium (Li) effects on motor activity with its brain concentrations in rats was studied. After administration of lithium chloride, motor activity gradually decreased until the maximum effect of the doses were observed after 8 hr; after which the activity returned to control levels in 48 to 72 hr. Li concentrations increased gradually reaching their peak at 8 hr in almost all brain areas except for the caudate nucleus where the peak level was at 12 hr. Other brain areas studied included cortex, hypothalamus, rest of the diencephalon, midbrain, pons medulla, and cerebellum. The time course of the depressant effect of Li on motor activity correlated with the changes in Li concentrations in the brain areas related to emotion and psychomotor activity. 16 references. (Author abstract modified)

003436 Nistico, G. Institute of Pharmacology, II Faculty of Medicine, University of Naples, Naples, Italy **Effects of Gaba, Gabob and some anticonvulsant drugs on dibutyryl cyclic AMP evoked seizures.** International Journal of Clinical Pharmacology and Biopharmacy (Munchen). 15(1):19-22, 1977.

The effects of gamma-aminobutyric acid (GABA), GABOB, phenobarbital, phenytoin and diazipam, given systemically, on convulsant activity evoked in chicks by intrahypothalamic injection of dibutyryl cyclic adenosine monophosphate (cAMP) were studied. Phenytoin and phenobarbital antogonized the effect of dibutyryl cAMP but the effects of GABA and GABOB were complicated by osmotic effects. Diazepam had no effect on dibutyryl cAMP induced electrocortical spiking. It is suggested that the dibutyryl cAMP induced syndrome is of limited value as a model for assessing the activity of anticonvulsant drugs. 14 references. (Author abstract modified)

003437 Oka, T.; Hosoya, E. Department of Pharmacology, School of Medicine, Tokai University, Isehara, Kanagawa 259-11, Japan **The different effect of humoral modulators on the morphine- and central nervous system stimulant-induced hyperactivity of rats.** Neuropharmacology (Oxford). 16(2):115-119, 1977.

The effects of humoral modulators on the increase in locomotor activity produced in rats by morphine, methamphetamine, caffeine or cocaine were investigated. Pretreatment of rats with alpha-methyl-para-tyrosine, atropine, methylatropine, scopolamine or methscopolamine significantly inhibited morphine induced increases in locomotor activity. Hyperactivity induced by methamphetamine, caffeine, or cocaine was attenuated by alpha-methyl-para-tyrosine, augmented by atropine or scopolamine, and unaffected by methylatropine or methscopolamine. It is suggested that the activity increasing effects of morphine in rats are mediated by mechanisms different from those which mediate the activity increasing effects of methamphetamine, caffeine, or cocaine in rats and from those which mediate the previously reported morphine induced hyperactivity in mice. 32 references. (Author abstract modified)

003438 Ozawa, Hikaru; Miyauchi, Tatsuo. Department of Pharmacology, Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan **Potentiating effect of lithium chloride on methamphetamine-induced stereotypy in mice.** European Journal of Pharmacology (Amsterdam). 41(2):213-216, 1977.

A single administration of LiCl was found to potentiate the methamphetamine induced stereotypy in mice, without affecting the concentration of methamphetamine in the brain. During MAO inhibition the level of 3-methoxytyramine (3-MT), an O-methylated metabolite of dopamine, was reduced by LiCl, but the elevated 3-MT level observed after the administration of methamphetamine was not influenced by LiCl. 10 references. (Author abstract modified).

003439 Peachey, J. E.; Rogers, B.; Brien, J. F. Addiction Studies Unit, Department of Psychiatry and Pharmacology, Queen's University, Kingston, Ontario K7L 3K1, Canada **A comparative study of the behavioural responses induced by chronic administration of methamphetamine and amphetamine in mice.** Psychopharmacology (Berlin). 51(2):137-140, 1977.

The behavioral effects induced in mice by chronic administration of dextromethamphetamine (MA) and dextroamphetamine (A) at three dosage levels were compared. MA exerted greater central excitation than A. At 0.64mg/kg,

quiescence was decreased and activity increased more by MA than by A. Hyperactivity induced by 2.5mg/kg was sustained over a longer time period with MA. Frenzied selftearing occurred more frequently in MA treated animals than in A treated animals with doses of 10mg/kg. 19 references. (Author abstract modified)

003440 Pickworth, W. B.; White, R. P. NIDA Addiction Research Center, P.O. Box 12390, Lexington, KY 40511 **Tryptamine: biomodal actions on the EEG and behavior of rabbits.** Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 225(1):64-76, 1977.

The bimodal actions of tryptamine on the EEG and behavior were investigated via the analysis by inspection and amplitude integration (electrogenesis) of EEG tracings from conscious restrained rabbits. Intravenously, tryptamine in doses of 0.1and 0.5mg/kg increased electrogenesis, whereas 1mg/kg initially decreased and subsequently increased electrogenesis. Higher doses always caused an immediate and dose dependent decrease in electrogenesis. Neither atropine or reserpine pretreatment prevented this decrease, whereas chlorpromazine and methysergide abolished it. Intravenous infusions of tryptamine at 1mg/kg/min caused a nonsignificant increase in electrogenesis but 2 and 4mg/kg/min infusions caused a sustained decrease. These results show that tryptamine has a biphasic effect on the cortical EEG: low doses enhance synchrony while high doses alert the EEG. Moreover, analysis of the behavioral, EEG, and peripheral effects of tryptamine indicate that different sites of action account for the multiple responses observed. Chlorpromazine and methysergide selectively inhibit the excitatory responses. It was concluded that the findings support the concept that tryptaminergic mechanisms are involved in abnormal posture behavior. 28 references. (Author abstract)

003441 Poling, Alan; Thompson, Travis. Psychiatry Research Unit, University of Minnesota Medical School, Box 392, Mayo Memorial Building, Minneapolis, MN 55455 **The effects of delta-amphetamine on the automaintained key pecking of pigeons.** Psychopharmacology (Berlin). 51(3):285-288, 1977.

The effects of three doses of delta/amphetamine on automaintained key pecking by pigeons when the percentage of occasions on which 8 second key illumination was followed by food delivery was successively decreased from 100% to 50%, 25%, 10%, and 2.5% were determined. Three food deprived pigeons were tested. Despite the lack of a programmed contingency between keypecking and food delivery or key illumination, keypecking occurred under all automaintenance conditions. Mean responses per 8 second key illumination during nondrug sessions varied from over 15 to less than one, with 100% and 50% pairing conditions engendering the highest rates and the 2.5% pairing condition the lowest. Under all automaintenance conditions, delta/amphetamine in doses of 0.5mg/kg, 1mg/kg, and 2mg/kg decreased responding in a dose related fashion. Rate/dependent effects were not evident despite the appreciable differences in mean response rates engendered by the various conditions. 27 references. (Author abstract modified)

003442 Poling, Alan; Thompson, Travis. Psychiatry Research Unit, University of Minnesota Medical School, Minneapolis, MN 55455 **Effects of delaying food availability contingent on ethanol-maintained lever pressing.** Psychopharmacology (Berlin). 51(3):289-291, 1977.

The effects of delaying food availability 8 seconds contingent on every lever press, every second lever press, and every fourth lever press maintained by 4%, 8%, and 16% ethanol solutions were examined when food was initially available to six adult male rats on a fixed-interval 26 second schedule. The delay contingency decreased ethanol maintained responding at all ethanol concentrations, with the degree of decrease inversely related to the intermittency of the delay schedule and to the ethanol concentration. Such decreases were not evident in the performance of yoked control animals which received food coincidentally with experimental animals. Temporal changes in food presentation alone therefore could not account for the decreases produced by the delay contingency. 6 references. (Author abstract modified)

003443 Price, M. T. C.; Murray, G. N.; Fibiger, H. C. Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, Vancouver, B.C. V6T 1W5, Canada **Schedule dependent changes in operant responding after lesions of the dorsal tegmental noradrenergic projection.** Pharmacology Biochemistry and Behavior. 6(1):11-15, 1977.

Schedule dependent changes in operant responding after lesions of the dorsal tegmental noradrenergic bundle (DTNB) in rats were studied in operant responding for food under various schedules of reinforcement. Bilateral stereotaxic injections of 6-hydroxydopamine into the DTNB of rats reduced hippocampal/cortical noradrenaline to less than 5% of control levels. Animals with these lesions acquired a continuously reinforced (CRF) bar-press response at the same rate as controls. Compared to controls rats with DTNB lesions responded at significantly lower rates on a variable interval 30 (VI 30) schedule. Extinction after VI 30 responding did not differ significantly between control and lesioned animals. In another experiment no significant difference was observed between DTNB lesioned and control groups on the rate of responding on a fixed ratio 30 (FR 30) schedule. The results are discussed with reference to previous reports indicating changes in operant responding after intraventricular injections of 6-hydroxydopamine. The data failed to support the hypothesis that the DTNB is critically involved in learning and memory. 27 references. (Journal abstract modified)

003444 Prop-Van den Berg, C. M.; Schuurman, T.; Wiepkema, P. R. Zoological Laboratory, University of Groningen, Haren, The Netherlands **Nembutal treatment of the VMH (rat): effects on feeding and sexual behaviour.** Brain Research (Amsterdam). 126(3):519-529, 1977.

The effects of Nembutal treatment of the ventromedial hypothalamic (VMH) nucleus on feeding and sexual behavior were studied in 17 male rats. Two brain cannulae were implanted bilaterally and directed to an area just dorsal of the VMH nucleus. The behavior of these animals was observed before and after the injection through these cannulae of either saline or Nembutal. Injections were performed under three behavioral conditions: 1) animal alone in cage with food; 2) animal in the presence of an estrous female; and 3) animal in cage with food and estrous female. Following the Nembutal injection, sniffing and feeding were disinhibited temporarily in condition 1, whereas in condition 3 only sniffing, but not feeding, is disinhibited. In conditions 2 and 3 male sexual behavior is not influenced by the Nembutal except for an increase of sniffing at the female. It is concluded that a temporary elimination of the VMH leads to a disinhibition of feeding only if the external conditions are favorable for feeding. The same elimination of the VMH does not influence the occurrence of male sexual behavior under the conditions used in these experiments. 28 references. (Author abstract)

003445 Pryor, G. T.; Husain, S.; Larsen, F.; McKenzie, C. E.; Carr, J. D.; Braude, M. C. Stanford Research Institute, Menlo Park, CA 94025 and National Institute on Drug Abuse, Rockville, MD 20852 **Interactions between delta9-Tetrahydrocannabinol and Phencyclidine Hydrochloride in rats.** Pharmacology Biochemistry and Behavior. 6(1):123-136, 1977.

Interaction of the depressant properties of delta9-Tetrahydrocannabinol (THC) and phencyclidine hydrochloride (PCP) in rats was studied using a variety of behavioral and physiological measures. THC impaired avoidance and rotarod performance, and caused bradycardia and hypothermia. PCP impaired avoidance and rotarod performance and caused a marked increase in photocell activity. When combined, the depressant properties of each drug were enhanced and the stimulation of photocell activity caused by PCP was antagonized by THC. Tolerance to many of the effects of 10.0mg/kg THC and its interactions with PCP followed subacute treatment for six days, whereas many of the effects of PCP were enhanced after subacute treatment with a dose of 2.5mg/kg. Open-field behavior was affected by each drug alone and in combination in a similar way as photocell activity, but the depression caused by their interaction was greater; both drugs caused an increase in urination. Response rates on an FR-10 schedule of food reinforcement were decreased by 2.5mg/kg PCP, but not by 5.0mg/kg THC; the combination caused greater response suppression than either drug alone. The functional interactions between THC and PCP were not related to changes in the concentrations of 14C or 3H in plasma or brain derived from 14C-THC and 3H-PCP, respectively. 87 references. (Journal abstract modified)

003446 Pycock, C. J.; Marsden, C. D. University Dept. of Neurology, Institute of Psychiatry, Denmark Hill, London SE5 8AF, England **Central dopaminergic receptor supersensitivity and its relevance to Parkinson's disease.** Journal of the Neurological Sciences (Amsterdam). 31(1):113-121, 1977.

The effects of chronic administration of levodopa on striatal dopamine receptor sensitivity, as judged by drug induced circling behavior, were assessed in mice with unilateral destruction of one nigroneostriatal dopaminergic pathway. Two groups of 20 lesioned mice each received levodopa starting 10 days postoperatively. The number of full circles completed by each animal in a 1 minute period was observed 30 minutes after levodopa administration. One group was then given dietary levodopa and carbidopa, while the second was fed only carbidopa for 2 months. All animals were tested for spontaneous circling behavior at weekly intervals. Results reveal that long-term oral administration of levodopa failed to influence dopaminergic receptor denervation supersensitivity. The relevance of these findings to the treatment of Parkinson's disease is discussed. 18 references.

003447 Ramaekers, F.; Rigter, H.; Leonard, B. E. Pharmacology Department, Scientific Development Group, Organon Int. B.V., Oss, The Netherlands **Parallel changes in behaviour and hippocampal serotonin metabolism in rats following treatment with desglycinamide lysine vasopressin.** Brain Research (Amsterdam). 120(3):485-492, 1977.

Changes occurring in behavior and hippocampal serotonin metabolism in rats following treatment with desglycinamide lysine vasopressin were investigated. Application of a footshock during the acquisition trial of a one trial passive avoidance task is associated with a rise in the concentration of serotonin in the hippocampus 24 hours after conclusion of the acquisition trial. Carbon dioxide (CO2) induces amnesia for the passive avoidance response when administered immediately upon termination of the acquisition trial. In rats subjected to CO2 treatment following footshock the rise in hippocampal serotonin is not observed 24 hours later. The vasopressin analogue desglycinamide lysine vasopressin attenuates CO2 induced amnesia for the passive avoidance response when given prior to either the acquisition or the retrieval test (24 hours after acquisition). This attenuation of the passive avoidance response is associated with a rise in the hippocampal serotonin concentration similar to the one observed in nonamnesic animals. It is suggested that a correlation exists between changes in hippocampal serotonin metabolism and the retrievability of the passive avoidance response. 12 references. (Author abstract modified)

003448 Ranje, Christer; Ungerstedt, Urban. Department of Histology, Karolinska Institutet, Stockholm, Sweden **Discriminative and motor performance in rats after interference with dopamine neurotransmission with spiroperidol.** European Journal of Pharmacology (Amsterdam). 43(1):39-46, 1977.

To investigate discriminative and motor performance in rats after interference with dopamine neurotransmission with spiroperidol, an underwater swim maze was developed which partly counteracts the akinesia of the animals. The disruption of instrumental conditioning after block of central dopamine neurotransmission with drugs or lesions has been explained as an inability to initiate movements rather than as a disruption of learning mechanisms per se. The maze has been used to test the effect of dopamine receptor inhibition by spiroperidol on a brightness and a spatial discrimination task. Acquistion was blocked and the behavior randomized after 0.05mg/kg and higher doses. Swim speed, however, was not affected by 0.05mg/kg. This suggests that spiroperidol affects the acquisition of this brightness discrimination task independently of its effects on motor performance. Spatial acquistion was not affected even at 5.0mg/kg which shows that the deficit can not be generalized to all types of acquistion. 21 references. (Author abstract modified)

003449 Rastogi, R. B.; Lapierre, Y. D.; Singhal, R. L. Department of Pharmacology, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, K1N 9A9, Canada **Evidence for the role of brain norepinephrine and dopamine in "rebound" phenomenon seen during withdrawal after repeated exposure to benzodiazepines.** Journal of Psychiatric Research (Oxford). 13(2):65-75, 1977.

Evidence for the role of brain norepinephrine (NE) and dopamine (DA) in rebound phenomena seen during withdrawal after benzodiazepine exposure is presented. The influence of repeated exposure to and subsequent withdrawal from diazepam and bromazepam treatment was studied on precursor tyrosine as well as the levels of NE, DA, and its metabolites, homovanillic acid and 3,4-dihydroxyphenylacetic acid in rat brain. Administration of diazepam and bromazepam for 22 days suppressed spontaneous locomotor activity but produced no change in bodyweights and striatal tyrosine levels. Chronic therapy with either anxiolytic agent significantly enhanced the concentration of NE and DA in several regions of the brain. In contrast, treatment decreased levels of striatal homovanillic acid. Data suggest that these benzodiazepines may manifest their taming effects by decreasing the physiological release and subsequent lowering of catecholamines in the vicinity of corresponding receptors. Forty eight hour withdrawal from benzodiazepines elevated the spontaneous locomotor activity significantly. Furthermore, levels of NE and DA were significantly decreased in regions of the brain, presumably due to massive release of these neurohumors. Withdrawal also

enhanced levels of striatal homovanillic acid, which is formed as a result of extraneuronal metabolism of DA. It is suggested that results may constitute a neurochemical basis for the role of DA and possibly NE in rebound phenomena seen clinically and in laboratory animals during the withdrawal phase from benzodiazepine therapy. 34 references. (Author abstract modified)

003450 Razzak, Abdul; Fujiwara, Michihiro; Oishi, Ryozo; Ueki, Showa. Department of Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq **Possible involvement of a central noradrenergic system in automutilation induced by clonidine in mice.** Japanese Journal of Pharmacology (Kyoto). 27(1):145-152, 1977.

To determine whether noradrenergic mechanisms play a role in inducing automutilation as well as aggression, a series of experiments in which automutilation was induced in male mice by intraperitoneally injected clonidine was undertaken. Automutiliation induced by a single large dose of clonidine was potentiated by pretreatment with methamphetamine, caffeine and theophylline, while it was inhibited by acute administration of reserpine alpha-methyl-p-tyrosine, phenoxybenzamine, phentolamine and chlorpromazine. L-Dopa, 5-hydroxytryptophan and p-chlorophenylalanine had no effect on this abnormal behavior. Biochemical studies on brain monoamines revealed that noradrenaline was markedly increased and dopamine slightly so, but 5-hydroxytryptamine was never changed by clonidine. These results suggest that a central noradrenergic system may be involved in automutilation induced by clonidine in mice. 25 references. (Author abstract)

003451 Rezek, M.; Havlicek, V.; Hughes, K. R.; Friesen, H. Department of Physiology, University of Manitoba, Faculty of Medicine, Winnipeg, Manitoba R3E 0W3, Canada **Behavioural and motor excitation and inhibition induced by the administration of small and large doses of somatostatin into the amygdala.** Neuropharmacology (Oxford). 16(3):157-162, 1977.

The effects of administration of several doses of somatostatin (somatotropin release inhibiting factor, SRIF) into the amygdala on motor control, EEG pattern and sleep/waking cycle were examined in rats. Lower doses of SRIF generally induced a behavioral excitation accompanied by a variety of tremors and stereotyped movements. Higher doses prevented the expression of a normal behavioral pattern by causing severe disturbances in motor control. The duration of rapid eye movement (REM) sleep showed a consistent dose related reduction although total sleeping time was not considerably altered. This was due to a paradoxical dose related prolongation of shallow slow wave sleep (drowsiness) which typically accompanied the periods of immobilization caused by motor control difficulties. This was often reflected in a paradoxical pattern characterized by a dissociation of EEG from behavior. Administration of some endocrinologically active analogues and inactive analogues of SRIF via the same route did not produce effects comparable to those produced by administration of the same dose of the endogenous substance. 11 references. (Author abstract modified)

003452 Rodin, E.; Kitano, H.; Nagao, B.; Rodin, M. Lafayette Clinic, 951 East Lafayette, Detroit, MI 48207 **The results of penicillin G administration on chronic unrestrained cats: electrographic and behavioral observations.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(4):518-527, 1977.

The production of seizures by penicillin G administration to 27 chronic unrestrained cats is described electrographically and clinically. The results showed that spike wave type activity occurred earliest in the cortex. The discharges were also best formed in cortical and thalamic structures. The other deep structures showed characteristic bursting, but not of the spike wave type variety. The cerebellum also showed early participation. Clinical expressivity of the bursts depended upon the state of alertness of the animal, the height of the spike components and the extent of depth participation. The high frequency recordings revealed characteristic alternation of decrease and increase in activity mostly in cortical structures and to a lesser extent in thalamus. Pontine and medullary reticular formation areas usually showed no changes in the high frequency records during the bursts. When major seizures were induced, they were always of focal onset rather than of the primary generalized type as one sees with pentylenetetrazol. Different cortical or deep structures served as the initiating site in different animals. It is concluded that systemic penicillin administration does not lead to a truly primary generalized form of epilepsy, but produces its effects by multifocal activation of various cerebral structures, with cortex and cerebellum usually showing earliest involvement. 18 references. (Author abstract modified)

003453 Rosenberg, Phyllis; Halaris, Angelos; Moltz, Howard. Committee on Biopsychology, Department of Behavioral Sciences and Psychiatry, University of Chicago, Chicago, IL 60637 **Effects of central norepinephrine depletion on the initiation and maintenance of maternal behavior in the rat.** Pharmacology Biochemistry and Behavior. 6(1):21-24, 1977.

The catecholaminergic neurotoxin, 6-hydroxydopamine (6-OHDA), was used to test the hypothesis that increased transmission across selected noradrenergic synapses is involved in the initiation of maternal behavior in the rat. 6-OHDA was infused intraventricularly either two days before parturition or four days after parturition. Control animals were infused with the vehicle alone. Among prepartum animals, norepinephrine (NE) depletion of more than 30 percent of control levels interfered with the initiation of maternal behavior. Among lactating animals, similar degrees of NE depletion had no significant effect on the maintenance of maternal behavior. Thus, NE appears to be involved in the initiation of maternal behavior, but not in the maintenance of the behavior once that behavior is established. 8 references. (Journal abstract)

003454 Sahakian, B. J.; Robbins, T. W. Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge, CB2 3EB, England **Isolation-rearing enhances tail pinch-induced oral behavior in rats.** Physiology & Behavior. 18(1):53-58, 1977.

Rats reared in groups and in isolation since weaning were studied in a control experiment and after the injection of alpha-flupenthixol, a dopaminergic (DA) receptor blocking agent, to compare the acquisition and performance of tail pinch (TP) induced oral behavior. Rats reared in isolation showed shorter latencies than group reared rats to initiate induced oral behavior such as eating, gnawing, or licking, whether tested at 33 or 49 days of age. Isolation reared rats were less susceptible to the inhibitory effects of alpha-flupenthixol. This drug was more effective in counteracting the acquisition, rather than the performance, of TP induced behavior. The results are discussed in terms of explanations of behavioral abnormalities of isolation reared rats based on theories of arousal and their possible mediation by the DA neurotransmitter system. It is suggested that the results support the hypothesis that isolation rearing enhances the functional activity of the DA system, but the behavioral mechanisms un-

derlying the effects remain unclear. 26 references. (Author abstract modified)

003455 Samanin, R.; Bendotti, C.; Bernasconi, S.; Borroni, E.; Garattini, S. Istituto di Ricerche Farmacologiche Mario Negri, Via Eritrea 62, I-20157 Milano, Italy **Role of brain monamines in the anorectic activity of mazindol and d-amphetamine in the rat.** European Journal of Pharmacology (Amsterdam). 43(2):117-124, 1977.

A study of the role of brain monoamines in the anorectic activity of mazindol and d-amphetamine in the rat is described. At each dose used, both compounds markedly counteracted the decrease of brain noradrenaline induced by 6-hydroxydopamine while only at high doses they did significantly reduce the effect of 6-hydroxydopamine on brain dopamine. Unlike d-amphetamine, mazindol significantly counteracted the decrease of brain serotonin induced by fenfluramine. The anorectic effect of mazindol and of d-amphetamine was markedly reduced by an electrolytic lesion at the level of the ventral noradrenergic bundle but not by an electrolytic lesion of the nucleus raphe medianus. An intrastriatal injection of 6-hydroxydopamine significantly reduced the effect of mazindol but not that of d-amphetamine. The results indicate that both compounds block noradrenaline uptake in the brain while their effect on dopamine uptake is less evident. Unlike d-amphetamine, mazindol appears to inhibit serotonin uptake also. In addition, the integrity of the noradrenergic neurons in the brain appears to be an important condition for these drugs to exert their anorectic effect. 42 references. (Author abstract)

003456 Sastry, B. S. R.; Sinclair, J. G. Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, V6T 1W5, British Columbia, Canada **Tonic inhibitory influence of a supraspinal monoaminergic system on presynaptic inhibition of an extensor monosynaptic reflex.** Brain Research (Amsterdam). 124(1):109-120, 1977.

Unanesthetized decerebrate cats (N=12) were administered imipramine HCl, 5-hydroxytryptophan, and a specific 5-hydroxytryptamine (5-HT) neuronal uptake blocker, fluoxetine HCl to investigate tonic inhibitory influence of a supraspinal monoaminergic system on presynaptic inhibition of an extensor (quadriceps, QUAD) monosynaptic reflex (MSR). The antagonism of the presynaptic inhibition of the QUAD MSR produced by imipramine and fluoxetine was partially reversed by cyproheptadine and completely reversed by the application of a thoracic cold block. Imipramine failed to antagonize QUAD MSR inhibition in animals pretreated with parachlorophenylalanine (PCPA) or alpha-methyl-paratyrosine methyl ester hydrochloride (AMPT). Cyproheptadine, phenoxybenzamine and a cold block enhanced the inhibition of the extensor MSR but a cold block failed to alter the inhibition in animals pretreated with PCPA or AMPT. Presynaptic inhibition of the flexor (posterior biceps semitendinosus, PBST) MSR was not affected by any of the treatments. The effects of the drugs tested and of a cold block on the excitability of the QUAD group Ia afferents were reciprocal to those on the MSR during presynaptic inhibition. It is concluded that the descending tonically active systems involving 5-HT and noradrenaline: 1) antagonize presynaptic inhibition of the QUAD MSR but not the PBST MSR; 2) decrease the excitability of the QUAD Ia afferents; and 3) increase the excitability of QUAD motoneurons. 24 references. (Author abstract modified)

003457 Schaefer, Gerald J.; Holtzman, Stephen G. Biological Psychiatry Research Unit, Room 504 North, Georgia Mental Health Institute, 1256 Briarcliff Road, NE, Atlanta, GA 30306 **Discriminative effects of morphine in the squirrel monkey.** Journal of Pharmacology and Experimental Therapeutics. 201(1):67-75, 1977.

Discriminative properties of morphine were studied in the squirrel monkey to extend similar investigations previously conducted in the rat. Squirrel monkeys were trained in a two choice discrete trial avoidance task to discriminate between intramuscular injections of saline and 3.0mg/kg of morphine. Morphine (0.1to 10mg/kg) produced a dose related increase in the number of trials completed on the morphine appropriate lever. The stimulus control produced by the discriminative effects of morphine met the following criteria for classification as a specific narcotic effect: 1) morphine-like stimulus control was produced by all other narcotic analgesics tested (fentanyl, oxymorphone, levorphanol, methadone and meperidine); 2) in so doing, these drugs spanned a 900 fold potency range relative to morphine; 3) stimulus control was blocked by the specific narcotic antagonist naloxone; and 4) stereospecificity was a requirement for stimulus control -- levorphanol produced stimulus control equivalent to 3.0mg/kg of morphine but its optical isomer dextrorphan did not. The time course of the stimulus control produced by 3.0mg/kg of morphine showed that the animals continued to respond on the morphine appropriate lever up to 14 hours after morphine administration. In contrast, monkeys administered 0.01mg/kg of fentanyl responded on the morphine lever for only as long as 1/2 hour after fentanyl administration. Naloxone, d-amphetamine and pentobarbital all failed to substitute for morphine. This study has extended previous observations of the discriminative properties of morphine in rats by demonstrating that qualitatively similar data are produced in a second species, the squirrel monkey. 35 references. (Journal abstract modified)

003458 Schmidt, Hans, Jr.; Butzer, Thomas. Department of Psychology, Xavier University, Cincinnati, OH 45207 **Phenobarbital drinking curves after varied water deprivation.** Pharmacology Biochemistry and Behavior. 6(2):243-244, 1977.

The effect of an extended range of phenobarbital doses on drinking after different degrees of water deprivation was studied in 16 rats. Phenobarbital dose/drinking response curves were obtained for 11 1/2 and 23 1/2 hr of water deprivation. Results indicated that the same quadratic curve was found in both cases displaced as a function of degree of deprivation. Results are explicable by regarding phenobarbital as an adequate stimulus for drinking or by disinhibiting drinking if level of inhibition is not directly concerned with regulation of water ingestion per se. The response to phenobarbital on days following injection is similar for both degrees of deprivation investigated. 6 references. (Author abstract)

003459 Schmidt, W.; Apfelbach, R. Universitat Tubingen, Lehrbereich Zoophysiologie, Auf der Morgenstelle 28, D-7400 Tubingen, Germany **/Psychopharmacological influence on the prey catching behavior of ferrets./** Psychopharmakologische Beeinflussung des Beutefangverhaltens beim Frettchen (Putorius furo L.). Psychopharmacology (Berlin). 51(2):147-152, 1977.

The effect of neuroleptics on the prey catching behavior of ferrets was studied. Haloperidol, clozapine, and chlorpromazine were administered to examine the central background and hierarchical structure of this behavior. Modification of predatory behavior was manifested in an improvement of orientation reactions when pursuing prey and in a better placement of bites. This effect was most evident with haloperidol. Clozapine delay prey approaching and, in some

cases, totally suppressed prey catching behavior. However, some behavioral elements, such as the use of paws, were unaffected by neuroleptics. 15 references.

003460 Shannon, Harlan E.; Holtzman, Stephen G. National Institute on Drug Abuse, Addiction Research Center, P.O. Box 12390, Lexington, KY 40511 **Further evaluation of the discriminative effects of morphine in the rat.** Journal of Pharmacology and Experimental Therapeutics. 201(1):55-66, 1977.

Discriminative effects produced by morphine in the rat were further investigated; analgesics with mixed agonist and narcotic antagonist properties were tested for their capacity to substitute for morphine, and the metabolite of morphine and structural analog of a narcotic analgesic in the benzomorphan series were tested to further assess the structural requirement for producing morphine-like discriminative effects. Rats were trained in a two choice discrete trial avoidance paradigm to discriminate between saline and 3.0mg/kg of morphine. Behavior was considered to be under stimulus control when the rats completed at least 90% of the trials in a 20 trial session on the morphine appropriate choice lever after receiving morphine and when they completed at least 90% of the trials on the saline appropriate choice lever after receiving saline. Of the narcotic antagonist analgesics tested, butorphanol and nalmexone produced discriminative effects equivalent to those of the morphine training dose whereas nalorphine, levallorphan, oxilorphan, nalbuphine and ketocyclazocine did not. The nonopioid psychoactive drugs, mescaline, ketamine, physostigmine and scopolamine, also failed to produce discriminative effects equivalent to those produced by 3.0mg/kg of morphine. These results confirm and extend previous findings that of those drugs which have also been evaluated in man, discriminative effects equivalent to the training dose of morphine are produced uniquely by narcotic analgesics and narcotic antagonists which produce morphine-like subjective effects. These results are compatible with the hypothesis that the properties of morphine which enable it to function as a discriminative stimulus in the rat are analogous to those responsible for producing subjective effects in man. 51 references. (Journal abstract modified)

003461 Sheard, Michael H.; Astrachan, David I.; Davis, Michael. Yale University School of Medicine, 34 Park Street, New Haven, CT 06508 **The effect of D-lysergic acid diethylamide (LSD) upon shock elicited fighting in rats.** Life Sciences (Oxford). 20(3):427-430, 1977.

Different doses of LSD were administered to male albino rats to investigate its effect on shock elicited fighting behavior. A biphasic dose response was found with low doses facilitating fighting and high doses having no effect. Since the effect of low doses in single cell studies is to specifically inhibit the presynaptic 5-hydroxy-tryptamine (5-HT) neuron, and thereby decrease impulse mediated release of 5-HT, the results are consistent with those experiments which show increased shock elicited fighting when brain 5-HT is lowered either by raphe lesions or p-chloroamphetamine (PCA). The fact that the high dose of LSD acted differently than the low doses may have occurred because the high dose of LSD also directly inhibited postsynaptic 5-HT neurons in addition to the presynaptic 5-HT neurons. In this case the postsynaptic agonistic effect may have effectively cancelled the excitatory effect resulting from inhibition of the presynaptic neurons. It is theorized that the enhanced motor activity actually interfered with well directed shock elicited fighting and this, rather than a direct stimulation of postsynaptic 5-HT neurons actually produced the nonmonotonic LSD dose response effect. 16 references. (Author abstract modified)

003462 Siegel, Shepard. Department of Psychology, McMaster University, Hamilton, Ontario L8S 4K1, Canada **Morphine tolerance acquisition as an associative process.** Journal of Experimental Psychology: Animal Behavior Processes. 3(1):1-13, 1977.

Morphine tolerance acquisition as an associative process was studied in rats. It was found that morphine analgesic tolerance is a manifestation of an association between the drug administration ritual and the systemic effects of the drug. Presenting environmental cues previously associated with morphine, but without the drug, attenuated established tolerance (i.e.,morphine tolerance can be extinguished). Repeated presentations of the morphine administration procedure, prior to its pairing with the opiate, retarded the acquisition of tolerance (i.e.,morphine tolerance is subject to "latent inhibition"). Placebo sessions interspersed between morphine sessions deleteriously affected the development of tolerance (i.e.,morphine tolerance is subject to the decremental effects of partial reinforcement). These findings appear inexplicable by most traditional theories of tolerance, which do not emphasize the role of drug associated environmental cues in the development of tolerance. It is suggested that the conditioning analysis of tolerance is congenial with a current view of habituation, and there may be a similar associative basis for the response decrement to both endogenous and exogenous iterative stimulation. 41 references. (Journal abstract)

003463 Stein, J. M.; Wayner, M. J.; Tilson, H. A. Brain Research Laboratory, Syracuse University, 601 University Avenue, Syracuse NY 13210 **The effect of para-Chlorophenylalanine on the intake of ethanol and saccharin solutions.** Pharmacology Biochemistry and Behavior. 6(1):117-122, 1977.

The effects of para-chlorophenylalanine (PCPA) on the ingestive behavior of rats offered a choice between ethanol (3%) and water, saccharin (0.125%) and water, or water alone were examined. Following a baseline period three saline or PCPA injections were administered. Decreases in both ethanol and saccharin intakes were observed. Increases in water intake occurred in the ethanol group without a change in total fluid intake. Increases in water intake did not occur in the saccharin group and these animals displayed decreases in total fluid intake. Water intake in the nonchoice group was unaffected. There were no changes in food intake associated with any of these effects. The data demonstrate that decreases in intakes following PCPA are not specific to ethanol solutions. 29 references. (Journal abstract modified)

003464 Stewart, W. J. no address **Effects of experience in the test environment on scopolamine-induced changes in activity in an exploration box.** Psychological Reports. 40(1):251-254, 1977.

The effects of experiences in the test environment on scopolamine induced changes in activity of rats in an exploration box were investigated. Saline and 0.25 mg/kg scopolamine treated rats (6 groups of 8) were tested under three conditions of experience (no experience, experience, and novel). Prior exposure affected scopolamine induced changes in ambulation, rearing, and grooming. 6 references. (Journal abstract modified)

003465 Stitzer, Maxine; McKearney, James W. Department of Psychiatry, D-S West Baltimore City Hospitals, 4940 Eastern Avenue, Baltimore, MD 21224 **Drug effects on fixed-interval responding with pause requirements for food presentation.** Journal of the Experimental Analysis of Behavior. 27(1):51-59, 1977.

Drug effects on fixed-interval responding with pause requirements for food presentation in pigeons is examined. Pentobarbital had effects on overall rates of responding consistent with a rate dependency interpretation, but dextroamphetamine either failed to increase low overall rates in the food delivery response (tandem DRL) components or increased them only slightly. Effects of both drugs on local responding within the fixed intervals were always related in an orderly way to control response rate, but the extent of rate increases produced by dextroamphetamine was modified in some birds by pause requirements such that the drug increased comparable rates less when these occurred in the tandem DRL component than when they occurred in the tandem DRH components. 19 references.

003466 Strombom, U.; Svensson, T. H.; Carlsson, A. Dept. of Pharmacology, University of Goteborg, Fack, S-400 33 Goteborg, Sweden **Antagonism of ethanol's central stimulation in mice by small doses of catecholamine-receptor agonists.** Psychopharmacology (Berlin). 51(3):293-299, 1977.

The effects of ethanol, the catecholamine (CA) receptor agonists (apomorphine, clonidine), and 3-hydroxybenzylhydrazine (NSD-1015)), and the agents in combinations on the rate of tryosine hydroxylation in different brain regions were investigated in female mice. Small doses of apomorphine caused a dose dependent suppression of the ethanol induced locomotor stimulation in mice and higher doses caused a delayed suppression. Very small doses of clonidine markedly suppressed the ethanol induced motor stimulation. Ethanol alone did not significantly affect the amount of Dopa accumulating in various mouse brain regions (limbic system, corpus striatum, hemispheres, and brainstem) during 30 minutes following administration of NSD-1015. Both the hypothermia and the locomotor stimulation by ethanol were antagonized by NSD-1015. The reduction in Dopa accumulation induced by a small dose of apomorphine in the dopamine rich regions in the mouse brain was slightly enhanced by ethanol, whereas the clonidine induced decrease in Dopa accumulation was, if anything, reduced. Thus, ethanol's behavioral stimulant action in mice can be largely suppressed by apomorphine or clonidine, drugs which in the small doses used probably inhibit central CA neurons. 40 references. (Author abstract modified)

003467 Symes, Aston L.; Lal, Samarthji; Young, Simon N.; Tsang, David; Sourkes, Theodore L. Department of Psychiatry, Montreal General Hospital, Montreal, Quebec, H3G 1A4, Canada **Effect of chronic chlorpromazine adminstration or prior treatment with reserpine on brain apomorphine concentrations and apomorphine-induced stereotyped behaviour in the rat.** European Journal of Pharmacology (Amsterdam). 43(2):173-179, 1977.

An investigation of the effect of chronic chlorpromazine administration or prior treatment with reserpine on brain apomorphine concentrations and apomorphine indiced stereotyped behavior in the rat is reported. Rats were pretreated with a single dose of reserpine or were given daily injections of chlorpromazine for 3 weeks. Controls received distilled water, 72 h after reserpine and 1 week after withdrawal from chlorpromazine, apomorphine was administered (10mg/kg, intraperitoneally). Both the intensity and duration of apomorphine induced stereotyped behaviour (ASB) and the concentration of apomorphine in brain were measured. Further groups of rats pretreated with reserpine or chlorpromazine as well as corresponding controls, received 0.25mg/kg apomorphine and the development of ASB was rated. Fourteen of 16 reserpine pretreated rats and 4 of 16 control rats developed ASB after 0.25mg/kg apmorphine. After withdrawal from chlorpromazine, apomorphine (0.25mg/kg) induced ASB in 12 out of 14 experimental and 5 out of 14 control rats. Following 10mg/kg of apomorphine there was a significant enhancement of motor activity associated with ASB in rats exposed to reserpine or withdrawn from chlorpromazine, compared to controls. This enhancement could not be explained by differences in brain apomorphine concentrations. The results are not inconsistent with the concept of neuroleptic induced supersensitivity of dopamine receptors. 13 references. (Author abstract)

003468 Tannen, Robert H.; Domino, Edward F. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109 **Exaggerated response to (+)amphetamine in geriatric gerbils.** Gerontology (Basel). 23(3):165-173, 1977.

Young adult (6 to 8 months) and old (greater than 24 months) gerbils were given (+)amphetamine intraperitoneally and were compared with respect to locomotor activity, body temperature, and toxicity. The old gerbils showed greater locomotor activity at 5.6mg/kg, greater hypothermia at 10.0mg/kg, and greater toxicity than the young adults. These differences were not found to be related to increased drug levels in whole blood or in the brain, or to diminished clearance of the drug from these sites. No age related difference was found in the ability to regulate body temperature in the face of extreme environmental temperatures, nor could a difference be detected in the hypothermic response to the dopaminergic againt apomorphine in doses of 5.6mg/kg intraperitoneally. 20 references. (Author abstract modified)

003469 Taub, Jonas; Taylor, Pamela; Smith, Martin; Kelley, Kim; Becker, Bruce; Reid, Larry. Bradley University, Peoria, IL 61606 **Methods of deconditioning persisting avoidance: drugs as adjuncts to response prevention.** Physiological Psychology. 5(1):67-72, 1977.

Methods of deconditioning persisting avoidance were tested in rats using drugs as adjuncts to response prevention. Rats were trained, across three daily sessions, to avoid intense footshock in an automated one-way avoidance box. Subsequent to training and termination of footshock, groups of rats received different treatments, and all were tested for persistence of avoidance 3 days later. One group's treatment was only handling, a no treatment group. All other groups were given response prevention, i.e. 10 min on the previously shocking grid without the opportunity to avoid. Groups of rats experienced response prevention under the influence of saline or doses of drugs: meprobamate, meprobamate in conjunction with atropine, atropine alone, atropine methyl nitrate, physostigmine, ethanol, morphine sulfate, amphetamine, chlordiazepoxide, and chlorpromazine. Only atropine led to reliably less persisting avoidance than response prevention controls, whereas doses of chlordiazepoxide led to more persisting avoidance. These data provide little support for the idea that widely used psychotropic drugs are effective in aiding the reduction of anxiety fear avoidance when postdrug behavior is the criterion for a drug's effectiveness. 33 references. (Author abstract)

003470 Tilson, H. A.; Chamberlain, J. H.; Gylys, J. A. Pharmacology Department, Bristol Laboratories, Syracuse, NY 13201 **Behavioral comparisons of R-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane (BL-3912A) with R-DOM and S-amphetamine.** Psychopharmacology (Berlin). 51(2):169-173, 1977.

The behavioral effects of R-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane (BL-3912A) were compared with those of

dextroamphetamine and R-2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane (R DOM) in rats. BL-3912A facilitated acquisition of shuttle box responding without increasing noncontingent intertrial (ITI) activity. Dextroamphetamine increased both avoidance responding and ITI responding. R DOM had a biphasic effect on avoidance responding, increasing it at low doses and disrupting it at higher doses. At doses that facilitated shuttle box responding, BL-3912A had no effect on unacclimated motor activity of rats nor on the rate of continuous avoidance responding. Dextroamphetamine increased the frequency of both motor activity and operant avoidance responding, while R DOM decreased motor activity and increased operant avoidance responding. By facilitating avoidance behavior without increasing other measures of psychomotor activity, BL-3912A represents a unique psychopharmacological agent clearly different from R DOM and dextroamphetamine. 9 references. (Author abstract modified)

003471 Tilson, Hugh A.; Chamberlain, John H.; Gylys, Jonas A.; Buyniski, Joseph P. NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709 **Behavioral suppressant effects of clondine in strains of normotensive and hypertensive rats.** European Journal of Pharmacology (Amsterdam). 43(2):99-105, 1977.

The behavioral effects of orally administered clonidine were investigated in Long-Evans (LE), Sprauge-Dawley (SD) or Kyoto Wistar (KW) rats assumed to be normotensive and in NIH spontaneously hypertensive (SH) rats. Although clonidine resulted in the same qualitative effect, i.e. depression of motor activity, the dose of clonidine required to depress motor activity to 50% of control levels (ED50) tended to vary according to strain. An analysis of variance of the dose response curves for the four strains of rats indicated a significant strain effect. When the effects of clonidine on food reinforced operant responding were investigated, it was observed that SD and SH rats differed with regard to rate and temporal patterning of IRT greater than 20 sec responding. Although oral administration of clonidine produced similar percentage decreases from control in SH and SD rats, an analysis of the temporal patterning of responding indicated differences in responsiveness to the behavioral effects of clonidine. These studies demonstrate strain related differences in responsiveness to the behavioral suppressant effects of clonidine. Marked differences between genetically hypertensive rats and rats assumed to be normotensive were not evident. 15 references. (Author abstract)

003472 Tokunaga, Yukiko; Muraki, Takamura; Hosoya, Eikichi. Dept. of Pharmacology, School of Medicine, Keio University, Shinjuku-ku, Tokyo 160, Japan **Effects of repeated morphine administration on copulation and on the hypothalamic-pituitary-gonadal axis of male rats.** Japanese Journal of Pharmacology (Kyoto). 27(1):65-70, 1977.

Adult male rats were administered morphine twice a day for 45 days and the effects of morphine on the copulation rate, the weight of various organs, and on the hypothalamic/pituitary/gonadal axis were examined. Morphine administered rats showed a loss of weight, hypertrophy of the adrenals, decreased weight of accessory sex organs, low sperm count, and decreased copulation rate. The contents of the luteinizing hormone releasing hormone in the hypothalamus and the luteinizing hormone in the pituitary remained unchanged. Serum luteinizing hormone and testosterone levels decreased, but serum follicle stimulating hormone levels increased. These results suggest that morphine inhibits the hypothalamic/pituitary/gonadal axis and causes a diminution in the number of fertilizations of the partner females. 10 references. (Author abstract)

003473 Tolosa, Eduardo S.; Cotzias, George C.; Burckhardt, Patricia G.; Tang, Lily C.; Dahl, Karen E. Medical Research Center, Brookhaven National Laboratory, Upton, NY 11973 **The dopaminergic and antidopaminergic effects of some aporphines.** Experimental Neurology. 55(1):56-66, 1977.

Experiments were conducted in mice to elucidate a mechanism by which two aporphines, apomorphine and N-n-propylnoraporphine, produce antagonistic effects to levodopa in Parkinson's disease patients and to dopamine mediated symptoms in other extrapyramidal disorders, and lose some of their pharmacological effects with repeated administration (tachyphylaxis). The evidence shows that unlike other aminergic drugs which also show tachyphylaxis, the dopaminergic effects of apomorphine and N-n-propylnoraporphine are not mediated through a presynaptic, dopamine releasing mechanism but through direct stimulation or dopamine receptors. Apocodeine, the methylated metabolite of apomorphine, exhibited weak dopaminergic effects but antagonized the dopaminergic effects of coadministered apomorphine on several behavioral tests and on the striatal adenylate cyclase of intact mice. It is concluded that the tachyphylaxis of both these aporphines and their antagonism to dopaminergic effects in patients might result from the accumulation at dopamine receptors of methylated metabolites of these aporphines which possess antidopaminergic properties. 31 references. (Journal abstract)

003474 Tsuchiya, T. Research and Development Center, Pharmaceuticals Division, Sumitomo Chemical Co., Ltd., 4-2-1, Takatsukasa, Takarazuka, Hyogo 665, Japan **Effects of 1,4-benzodiazepines with a long side chain in position 1 on the evoked potentials recorded in the limbic system and hypothalamus.** Neuropharmacology. 16(4):259-266, 1977.

The effects of 1,4-benzodiazepines with a long side chain in position 1 on the evoked potentials recorded in the limbic system and hypothalamus were compared to those of diazepam (DZ) in cats. The investigated drugs were ID-622, ID-495-37, and prazepam (PZ). Diazepam and ID-622 attenuated the hippocampal potential (HP) evoked by stimulation of the amygdala; ID-495-37 was effective at higher doses, but PZ had no effect. The amplitude of the ventromedial hypothalamic potential evoked by stimulation of the amygdala was increaed by DZ, ID-622 and ID-495-37, but not by PZ. The latency of the potential was not changed by any of the drugs. Only DZ significantly stimulated the amygdaloid potential evoked by stimulation of the ventromedial hypothalamus and increased the amplitude of the HP evoked by stimulation of the septum, but DZ decreased that of the potential evoked by stimulation of the ventromedial hypothalamus. The amplitude of the HP evoked by stimulation of the central gray matter was reduced by DZ, ID-622, and ID-495-37, but not by PZ. ID-622, and ID-495-37 exerted an action on the electroencephalogram similar to that of DZ, as they attenuated and slowed down the frequency of the hippocampal theta wave. 36 references.

003475 Tye, N. C.; Sahgal, A.; Iversen, S. D. Department of Psychology, Downing Street, Cambridge CB2 3EB, England **Benzodiazepines and discrimination behaviour: dissociation of response and sensory factors.** Psychopharmacology (Berlin). 52(2):191-194, 1977.

The effects of chlordiazepoxide and flurazepam on discrimination behavior in pigeons was studied by a new method which dissociated response and sensory factors. The pigeons were trained on a schedule which allowed concurrent measurement of motor and exteroceptive sensory changes. The task in-

volved a conditional color discrimination contingent upon the completion of a fixed interval (FI) schedule of responding. Both benzodiazepines enhanced perseverative responding (after completion of the FI), and to a variable degree responding during the FI, although there was no evidence for an increase in responding during the intertrial intervals. No marked changes in discrimination performance were observed. It was concluded that the most significant effects of these benzodiazepines are on motor mechanisms. 21 references. (Author abstract modified)

003476 Usui, Setsuo; Iwahara, Shinkuro. Department of Psychology, Tokyo University of Education, 3-29-1 Otsuka Bunkyoku, Tokyo, Japan **Effects of atropine upon the hippocampal electrical activity in rats with special reference to paradoxical sleep.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(4):510-517, 1977.

The influence of atropine sulphate on the hippocampal theta activity, with special emphasis on paradoxical sleep (PS), was studied in five freely moving male rats with implanted electrodes. In accordance with previous work with cats and rabbits, atropine was found to inhibit PS, in delaying its first appearance as well as in decreasing the duration of the first PS episode. The hippocampal theta activity during PS was also changed after atropinization. In particular, when REM occurred often, theta activity was increased not only in frequency but also in amplitude; however, with no or little REM, theta frequency was not changed but the regularity of theta rhythms was markedly disturbed. These findings are in contrast with the theta activity associated with gross body movement, which was not affected by atropine as previously reported by Vanderwolf (1975). Thus, in contrast to commonly held views, the hippocampal theta activity during gross body movement may be different in its underlying mechanisms from that during PS. 15 references. (Author abstract)

003477 Van Ree, Jan M.; De Wied, David. Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands **Modulation of heroin self-administration by neurohypophyseal principles.** European Journal of Pharmacology (Amsterdam). 43(2):199-202, 1977.

The influence of various neuropeptides related to neurohypophyseal hormones on initiation and maintenance of heroin self-administration in rats was studied. It was found that neuropeptides related to hypothalamic neurohypophyseal hormones affected intravenous heroin self-administration behavior in rats. Desglycinamide9, arginine8-vasopressin, and pressinamide reduced, while oxytocin and its C-terminal tripetide, prolyl-leucyl-glycinamide facilitated this behavior. The effectiveness of the vasopressin analogue appeared to be of a long-term nature. The data indicated a modulating effect of these principles on the reinforcing efficacy of heroin. 9 references. (Author abstract)

003478 Vogel, Wolfgang H.; Cohen, I. Dept. of Pharmacology, Thomas Jefferson University, Philadelphia, PA 19107 **Effects of tryptamine on the conditioned avoidance response in rats.** Brain Research (Amsterdam). 122(1):162-164, 1977.

The effects of tryptamine (TA) on the conditioned avoidance response (CAR) in rats with and without monoamine oxidase inhibition were studied, and the brain levels of TA during periods of abnormal behavior were determined. TA interferes with the CAR in rats if the animals are pretreated with iproniazid and TA is allowed to accumulate in the brain. The effects are those of a typical hallucinogenic compound. The effective dose is approximately 5mg/kg, and the brain level at the onset of abnormal behavior is approximately 0.5nmoles/g. A comparison of the potency of TA with dimethyltryptamine on the CAR shows that TA is a more potent psychoactive compound and that N-methylation decreases behavioral activity of TA. 15 references.

003479 Wachtel, H.; Anden, N.-E. Department of Pharmacology, University of Goteborg, S-400 33 Goteborg, Sweden **Effects on motor activity following local application of gamma-amino butyric acid (GABA) and GABA-like drugs into the rat nucleus accumbens.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R55, 1977.

Studies of the effects of local application on gamma-aminebutyric acid (GABA) and GABA-like drugs into the rat nucleus accumbens on motor activity are reported in a paper given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977. Bilateral administration of GABA or gamma-hydroxybutyric acid (GHBA) into the nucleus accumbens produced a brief dose dependent inhibition of motor activity. The initial motor depression produced by GHBA was followed by a phase of locomotor stimulation. The structurally related compounds carnitine and beta-hydroxybutyric acid were almost without influence on spontaneous motor activity. Pretreatment with the GABA transaminase inhibitor aminooxyacetic acid prolonged the effect of locally administered GABA. Bilateral administration of the putative GABA antagonist pictrotoxin produced a dose dependent stimulation of locomotor activity. The supposed glycine receptor antagonist strychnine and the general convulsant pentylenetetrazole had no effect on locomotor activity. It is suggested that the data indicate that a GABA mediated mechanism in the nucleus accumbens might interfere with the performance of locomotor activity in the rat. (Author abstract modified)

003480 Waddington, John L.; Olley, Jean E. Division of Psychiatry, MRC Clinical Research Centre, Watford Road, Harrow HA1 3UJ, England **Dissociation of the anti-punishment activities of chlordiazepoxide and atropine using two heterogeneous passive avoidance tasks.** Psychopharmacology (Berlin). 52(1):93-96, 1977.

The effects of chlordiazepoxide and atropine on the acquistion of passive avoidance learning in rats were compared in two superficially similar but theoretically distinct forms of the step down task in an attempt to dissociate behaviorally the disinhibiting effects of these two classes of drug. In a discrete trial procedure both chlordiazepoxide and atropine significantly retarded acquistion; on retention testing under saline treatment alone, the initial chlordiazepoxide group showed no change in behavior while the initial atropine group showed a facilitation. In a continuous trial procedure, however, atropine but not chlordiazepoxide produced an increase in the total number of step downs. Although these groups showed acquistion at similar rates, learning was not shown on retention testing under saline alone. These results enabled the two classes of drug to be distinguished. A fundamental difference between the discrete trial paradigm and the continuous trial paradigm in the nature of the punishment contingencies was noted. It is suggested that although both punishment and escape paradigms are potent in the acquistion of new behaviors and the alteration of old behavioral repertoires, there is no reason to equate them psychologically or physiologically and that the effects of differing compounds may be selectively dependent on differing parameters of the behavioral method of assessment. 17 references. (Author abstract modified)

003481 White, Norman; Sklar, Lawrence; Amit, Zalman. Dept. of Psychology, McGill University, 1205 McGregor St., Montreal, Quebec H3A 1B1, Canada **The reinforcing action of morphine and its paradoxical side effect.** Psychopharmacology (Berlin). 52(1):63-66, 1977.

Naive male rats (N=33) trained to run to a goalbox for food were tested 50 min after administration of morphine or lithium chloride to investigate the positive reinforcement and conditioned taste aversion (CTA) effects of the narcotic. Over five trials, rats that received morphine increased their running speed approximately 400% while the amount of food they ate in the goalbox decreased to about 70% of baseline values. The running speed of rats that received lithium chloride decreased to about 30%, while the amount of food they ate decreased to less than 10% of baseline. These two variables did not change for rats that received saline injections. The large increases in running speed observed in the rats that received morphine injections were attributed to an interaction between the positive reinforcing effects of morphine and food. 13 references. (Author abstract modified)

003482 Whitney, Glayde; Horowitz, Gary P.; Collins, Robert L. Florida State University, Tallahassee, FL 32603 **Relationship between morphine self-administration and the effect of morphine across strains of mice.** Behavior Genetics. 7(1):92, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, an ongoing project investigating preference of mice for morphine and the effects of morphine on behavior was described. In preference tests of saccharin taste masked morphine vs water, inbred strains of mice ranged from essentially complete avoidance of morphine to a strong preference for the morphine solution. Following intraperitoneal injection of morphine, there was a wide range of effect among inbred strains on analgesic and activity tests. Across six inbred strains that were tested for both preference and the effects of morphine, there was a strong positive relationship between preference and activity. Strains that avoid morphine do not become active following intraperitoneal injection of morphine, while strains that prefer morphine display heightened activity following morphine injection. (Author abstract modified)

003483 Will, Bruno E.; Sutter, Alain R.; Offerlin, Michael R. Laboratory of Psychophysiology, Louis Pasteur University, University Street, F-67000, Strasbourg, France **/Effects of methamphetamine and enriched experience on behavioral recovery after brain damage./** Effets de la methamphetamine et d'un environnement complexe sur la recuperation comportementale apres atteinte cerebrale. Psychopharmacology (Berlin). 51(3):273-277, 1977.

Two factorial experiments (brain status by environment by drug) were designed to measure the effects of methamphetamine and enriched experience on recovery after bilateral cortical lesions. Fisher male rats were operated or sham operated when 30 days old and thereafter raised in either an enriched or impoverished condition while daily injected with either methamphetamine or saline. In the enriched condition 12 rats lived together in a large cage with stimulus objects that were changed daily. In the impoverished condition a rat was kept alone in a small cage. The animals' performance was measured on a standard series of problems in a Hebb-Williams maze. The animals' scores were impaired by removal of tissue from the occipital cortex. Enriched experience helped significantly in overcoming, at least partially, the effects of brain damage on problem-solving behavior regardless of whether this experience was given for 2 hours a day over a 60 day period or for 2 hours a day over a 30 day period. No drug effect was found in any of the experiments. 19 references. (Journal abstract modified)

003484 Wise, Dale A.; Pryor, Toni L. Department of Psychology, San Jose State University, San Jose, CA 95192 **Effects of ergocornine and prolactin on aggression in the postpartum golden hamster.** Hormones and Behavior. 8(1):30-39, 1977.

The effects of prolactin (PRL) and ergocornine hydrogen maleate, an inhibitor of PRL secretion, on aggression were investigated in 38 female golden hamsters in the postpartum condition, which is associated with high levels of aggression and PRL. Three groups of ovariectomized and hysterectomized females were compared: normally lactating, ergocornine treated, and ergocornine plus replacement PRL treated. Normally lactating mothers were typically aggressive toward males in an arena, whereas females given ergocornine were not. Females given both ergocornine and PRL showed an intermediate level of aggression. Although ergocornine suppressed aggression toward adult males, attacks on pups increased. A second experiment sought to determine whether ergocornine would depress aggression when PRL involvement was unlikely. At least 30 days following pup removal, females from the first experiment were "trained" to attack home cage intruders consistently. After ergocornine administration, home cage attacks by these experienced females were not diminished. Since PRL levels were probably low in these animals, it is concluded that the effects of ergocornine on aggression were limited to instances in which PRL was involved, and that PRL probably can facilitate aggression. 19 references. (Author abstract)

003485 Wolfarth, Stanislaw; Kolasiewicz, Waclaw. Institute of Pharmacology, Polish Academy of Sciences, 31-344 Krakow, Poland **Effects of intrastriatal injections of atropine and methacholine on the apomorphine-induced gnawing in the rabbit.** Pharmacology Biochemistry and Behavior. 6(1):5-10, 1977.

To find out the anatomical location of the target point of cholinergic/dopaminergic equilibrium, atropine or methacholine were injected through previously implanted cannulas into various places of caudate nucleus and putamen of the rabbit, and the effect of the injections on stereotyped gnawing induced by subcutaneously or intravenously administered apomorphine was assessed. The intensity of gnawing was measured using a special apparatus, counting each bite. Atropine inhibited the sterotypy, while metacholine potentiated it. The effects were evident with the method used, but difficult to reveal with the classical method of assessing the intensity of stereotyped behavior, based on visual observation. The results suggest that the striatum is not a target point for the cholinergic component of the cholinergic/dopaminergic equilibrium in the central nervous system. 53 references. (Journal abstract)

003486 Wood, W. Gibson. Dept. of Psychology, Syracuse University, Syracuse, NY 13210 **Facilitation by dexamethasone of tolerance to ethanol in the rat.** Psychopharmacology (Berlin). 52(1):67-72, 1977.

Male rats (N=72) were tested in a Y-maze after administration of ethanol alone or with the snythetic glucocorticoid dexamethasone (DM) to test the hypothesis that the hypothalamic pituitary adrenal complex (HPAC) influences the development of tolerance to daily ethanol exposure. Rats injected daily with DM and ethanol showed an antagonism to the acute effects of ethanol and a higher rate of tolerance development to the depressant effect of ethanol than animals administered ethanol

only. Daily ethanol administration and adaptation to the testing environment facilitated the development of tolerance, compared to ethanol administration only. The results are discussed in relation to a possible stimulant effect of DM on behavior, an increase in the metabolism of ethanol, and a possible accumulation of DM in the brain producing an altered response to ethanol. 24 references. (Author abstract modified)

003487 Wood, W. Gibson; Schreiber, Henry L.; Villescas, Ramiro; Carlson, Richard H. Gerontology Research Laboratory, Syracuse University, 910 Irving Avenue, Syracuse, NY 13210 **Effects of prior experience and functional disturbance on acute and chronic tolerance to methylphenidate.** Psychopharmacology (Berlin). 51(2):165-168, 1977.

The hypothesis that animals with prior experience (habituation) in a test environment should show less drug induced behavior and more rapid development of tolerance when tested than do animals chronically injected with the drug but not tested until the last day was examined in rats. Methylphenidate was selected as the test drug in order to determine whether tolerance to its effects develops in rodents. Rats allowed to adapt in a Y-maze for 24 days showed less methylphenidate induced activity than animals receiving chronic administration of saline or methylphenidate, but no adaptation when tested in the Y-maze on day 25, suggesting support for the hypothesis. Tolerance to the methylphenidate induced activity was also demonstrated. 19 references. (Author abstract modified)

003488 Yanai, Joseph; Ginsburg, Benson E. Dept. of Physiology, University of Illinois at the Medical Center, P.O. Box 6998, Chicago, IL 60680 **Long term reduction of male agonistic behavior in mice following early exposure to ethanol.** Psychopharmacology (Berlin). 52(1):31-34, 1977.

Two discrete strains of mice (C57B2/10Bg and DBA/1Bg) were administered ethanol prenatally and neonatally to investigate induction of long-lasting neural and agonistic behavioral changes. Ethanol was administered to offspring through their parents who received 10% ethanol as their only liquid supply either before and during pregnancy, or from delivery until 14 days postpartim, or during both periods. Male agonistic behavior at age 50 days of the treated offspring was compared with pair fed controls. Early ethanol input resulted in a 23% increase in latency to attack in C57 mice and 58% in DBA, as well as a 49% (C57) and 38% (DBA) decrease in time spent fighting. The sensitive period to ethanol effect was apparently postnatal. Prenatal administration had no effect on agonistic behavior. DBA offspring were more aggressive than C57 and the scores of C57 offspring were more variable, thus indicating a lower phenotypic buffering in this strain. 25 references. (Author abstract modified)

003489 Zabik, J. E.; Levine, R. M.; Spaulding, J. H.; Maickel, R. P. Department of Pharmacology, Medical Sciences Program, Indiana University, Bloomington, IN 47401 **Interactions of tricyclic antidepressant drugs with deprivation-induced fluid consumption by rats.** Neuropharmacology. 16(4):267-271, 1977.

Six tricyclic antidepressant drugs, representing both secondary and tertiary amines and 4 different ring systems, were examined for the effects on deprivation induced fluid consumption by rats in a standardized test system. All compounds reduced fluid consumption with desipramine being the most potent, followed in order of potency by amitriptyline, doxepine, nortriptyline, imipramine and protriptyline. Alpha-methyltyrosine (AMT) either alone or followed by protriptyline treatment decreased brain norepinephrine (NE) levels by 66%, but did not affect serotonin (5-HT) levels. Protriptyline had no effects on brain NE or 5-HT levels. The reduction in fluid consumption in AMT and protriptyline rats was approximately additive. Para-chlorophenylalanine (CPA) reduced both 5-HT and NE on day 1, 5-HT alone on day 8, and neither by day 15. CPA reduced fluid consumption on the 1st day after CPA, but levels approached normal by the 3rd day. Administration of protriptyline on days 1, 8, or 15 after CPA evoked no additional reductions in fluid consumption; however the values observed were not significantly different from protriptyline alone on any of the 3 test days. 15 references.

003490 Zvartau, Edwin E. Department of Pharmacology, Pavlov Medical Institute, 197089 Leningrad, USSR **Hypothalamic self-stimulation under the chronic morphine treatment in the rat.** Research Communications in Chemical Pathology and Pharmacology. 16(4):707-719, 1977.

The influence of morphine on hypothalamic self-stimulation under chronic morphine administration (30 injections for 15 days) in increasing doses (from 20 to 120mg/kg/injection) has been studied in rats. Initial doses had a depressive effect varying in degree in different animals. Subsequent injections activated reward behavior. This activation is suggested as one of the neurophysiological mechanisms of morphine abuse and addiction. 13 references. (Author abstract modified)

05 TOXICOLOGY AND SIDE EFFECTS

003491 Blum, Kenneth; Briggs, Arthur H.; Feinglass, Sanford J.; Domey, Richard; Wallace, Jack E. Department of Pharmacology, University of Texas, Health Science Center at San Antonio, TX 78284 **Effects of delta9-tetrahydrocannabinol (delta9-THC) on amphetamine-aggregate toxicity in mice.** Current Therapeutic Research. 21(2):241-244, 1977.

The effect of delta9-tetrahydrocannabinol (delta9-THC) on amphetamine induced aggregate toxicity was investigated in mice. Our results indicate that delta9-THC appeared to have had a biphasic action with regard to amphetamine induced aggregate toxicity. Higher doses (3.0mg./kg.)add to the mortality, whereas lower doses (0.75 mg./kg.)reduce the mortality. These findings suggest that, at lower doses, delta9-THC may be depressant, but at higher doses, it may act as an excitant. 12 references. (Author abstract modified)

003492 Borodkin, Saul; Macy, Lowell; Thompson, George; Schmits, Ronald. Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064 **Stable nonagueous pentobarbital sodium solutions for use in laboratory animals.** Journal of Pharmaceutical Sciences. 66(5):693-695, 1977.

The degradation kinetics of pentobarbital sodium in propylene glycol based solutions were studied along with the in vivo effects in laboratory animals. The degradation rate constant was directly proportional to the water concentration in propylene glycol water solvent systems. An activation energy of 23.4kcal/mole was obtained in propylene glycol water (1:1). Pentobarbital sodium solutions in anhydrous propylene glycol and 9:1 mixtures of propylene glycol with ethanol, glycerin, or dimethylacetamide gave relatively slow degradation rates at 100 degrees, with all projected stability at 25 degrees greater than 4.5years. Intravenous administration of pentobarbital sodium in various anhydrous propylene glycol based vehicles to rats produced no hemolysis or gross organ damage that would interfere with pathological evaluations. Results of an intraperitoneal sleeptime study indicated that pentobarbital sodium produced consistent hypnotic effects when administered as an aqueous solution or in anhydrous

propylene glycol based vehicles. 8 references. (Author abstract)

003493 Burt, David R.; Creese, Ian; Snyder, Solomon H. Department of Pharmacology, University of Maryland School of Medicine, Baltimore, MD 21205 **Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain.** Science. 196(4287):326-328, 1977.

Dopamine receptor binding of (3H)haloperidol in the corpus striatum of rats was measured following chronic treatment with neuroleptic drugs to determine whether motor changes seen after such treatment are associated with an increase in the number of dopamine receptors. Chronic treatment of rats with the neuroleptic drugs haloperidol, fluphenazine, and reserpine elicits a 20 to 25% increase in striatal dopamine receptor binding assayed with (3H)haloperidol. This increase in receptor sites may account for behavioral supersensitivity to dopamine receptor stimulants in such animals and for tardive dyskinesia in patients treated with these drugs. 11 references. (Author abstract modified)

003494 Collins, Robert L.; Horowitz, Gary P.; Passe, Dennis H. Florida State University, Tallahassee, FL 32603 **Genotype and test experience as determinants of sensitivity and tolerance to morphine.** Behavior Genetics. 7(1):50, 1977.

In a paper presented at the Behavior Genetics Association meeting, Boulder, Colorado, June 1976, initial sensitivity and tolerance to the effects of morphine were studied in six inbred strains and one hybrid group of mice using both a hot plate analgesia test and a locomotor activity test. Three dose levels of morphine and one dose of saline were used to allow assessment of test experience effects on initial sensitivity and tolerance. Cross-genotype differences were obtained in initial sensitivity to morphine with both measures, and there were large effects of test experience differing in magnitude across genotypes. Tolerance to the effects of morphine developed differentially across genotypes with the analgesia test, but there was no evidence of tolerance with the activity measure for the same subjects with most strains showing greater sensitivity to morphine effects after repeated injections. It is recommended that effects of test experience be controlled in assessing morphine effects. (Author abstract modified)

003495 Das, M.; Ganguly, D. K. Division of Pharmacology, Indian Institute of Experimental Medicine, Calcutta 700022, India **Interactions of some cholinolytic anti-Parkinson drugs with nicotine and oxotremorine on rat diaphragm.** Toxicology and Applied Pharmacology. 39(1):149-152, 1977.

Interactions between the cholinoytic antiparkinson drugs cycrimine, benztropine, and biperiden, and the tremorogenic agents oxotremorine and nicotine were examined employing isolated phrenic nerve/diaphragm preparations in rats. Preincubation with the antiparkinson drugs prevented the impairment of neuromuscular transmission caused by oxotremorine and nicotine. The results indicate that the skeletal myoneural site may play a role in chemically induced Parkinson-like features in experimental animals, as well as in its prevention by the antiparkinson drugs. 19 references. (Author abstract)

003496 Doggett, N. S.; Reno, H.; Spencer, P. S. J. Department of Pharmacology, University of Wales, Institute of Science and Technology, Cardiff, Wales **A comparison of the acute toxicity of some centrally acting drugs measured under crowded and uncrowded conditions.** Toxicology and Applied Pharmacology. 39(1):141-148, 1977.

The acute toxicity of some centrally acting drugs was compared under crowded and uncrowded conditions. The acute toxicity of (+)-amphetamine in mice increases markedly under crowded conditions. Isocarboxazid, desmethylimipramine, naloxone, pethidine, and the dihydrocodeinone derivative RX 336M exhibit a similar although less marked effect. The dose except for lethality regression lines obtained under crowded conditions were parallel to those obtained under uncrowded conditions desmethylimipramine, cyclazocine, and the narcotic partial agonist RX 336M, which were all associated with nonparallel regression lines, possibly indicative of a stress induced change in the mechanism of the observed toxicity. Morphine exhibits multiphasic dose response curves under both crowded and uncrowded conditions which appear to be almost superimposable above 150mg/kg sc. It is concluded that the environmental conditions can markedly influence the acute toxicity of a wide range of drugs other than (+)-amphetamine, and consequently, care should be taken in any comparative studies. 29 references. (Author abstract)

003497 Domjan, Michael. Department of Psychology, Mezes 330, University of Texas, Austin, TX 78712 **Selective suppression of drinking during a limited period following aversive drug treatment in rats.** Journal of Experimental Psychology: Animal Behavior Processes. 3(1):66-76, 1977.

Selective suppression of drinking during a limited period following aversive drug treatment was studied in rats by the administration of lithium chloride. The lithium chloride disrupted the intake of flavored solutions but not water. This intake suppression was directly related to the amount of lithium administered (Experiment 1), occurred with both palatable and unpalatable novel saccharin solutions (Experiment 2), but was only observed if subjects were tested starting less than 75 min after lithium treatment (Experiment 3). Twenty five daily exposures to saccharin did not attenuate the effect (Experiment 4). However, in saccharin reared and vinegar reared rats, lithium did not disrupt consumption of the solutions these subjects had access to throughout life, even though suppressions of intake were observed when these subjects were tested with novel flavors (Experiment 5). The selective disruption of drinking is interpreted as a novelty dependent sensitization reaction to the discomfort of aversive drug administration. 22 references. (Journal abstract modified)

003498 Giusti, G. V.; Chiarotti, M.; Passatore, M. Universita Cattolica del S. Cuore, via della Pineta Sacchetti 644, I-00168 Roma, Italy **Muscular dystrophy in adult mice chronically treated with 9-THC at behavioral doses.** Experientia (Basel). 33(2):257-258, 1977.

The action of delta 9-tetrahydrocannabinol (THC) on the muscular development of 8 mice was tested. After chronic treatment with THC at behavioral dosed, a muscular dystrophy was demonstrated on the basis of histological and biochemical data and functional tests on muscle. It is not yet established whether the drug acts directly on the motor nerve terminals in the muscle or whether a more general mechanism is involved. 10 references. (Author abstract modified)

003499 Henderson, George I.; Schenker, Steven. Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37203 **The effect of maternal alcohol consumption on the viability and visceral development of the newborn rat.** Research Communications in Chemical Pathology and Pharmacology. 16(1):15-32, 1977.

From clinical observations that offspring of pregnant alcoholics are prone to congenital defects and abnormal growth

and development (fetal alcohol syndrome), the effects of long-term maternal alcohol intake on offspring viability and growth as well as the desoxyribosenucleic acid (DNA), total ribonucleic acid (RNA), protein levels, and DNA synthesis in brain, heart, liver, and kidney of 3-day-old newborn rats were investigated. Chronic oral intake of alcohol (mean 21 weeks plus 20 days of gestation) resulted in maternal blood alcohol levels of 67mg to over 150mg percent. There was a significant increase of newborn mortality and a decrease in body weight at 3 days in alcohol exposed compared to pair fed (nonalcohol exposed) controls. Protein concentration was unchanged in heart, liver, and kidney, and was slightly elevated in brain of 3 day old pups exposed to ethanol in utero. DNA synthesis rates were normal in all four organs, while DNA concentration was significantly lower only in the liver of the alcohol exposed group. In the alcohol exposed group, total RNA levels were significantly depressed in all four organs. Results suggest that prolonged maternal alcohol intake has an adverse effect on newborn rat viability and growth as well as the total RNA and to some extent DNA concentration of vital organs. 17 references. (Author abstract modified)

003500 Jacobs, Jean M.; Carmichael, N.; Cavanagh, J. B. MRC Research Group in Applied Neurobiology, Institute of Neurology, Queen Square, London WC1, England **Ultrastructural changes in the nervous system of rabbits poisoned with methyl mercury.** Toxicology and Applied Pharmacology. 39(2):249-261, 1977.

Ulturastructural changes in the nervous system of rabbits poisoned with methyl mercury are observed in order to confirm cell types affected. Rabbits were given methyl mercury acetate orally at a daily dose of 7.5mg/kg for from 1 to 4 days. Although dorsal root and Vth cranial nerve ganglion cells were the most sensitive, certain special cell types within the central nervous system were also susceptible. These included granule, stellate, and basket cells of the cerebellum and small neurons of the cerebral cortex. The features common to them are their relatively small size and high nuclear to cytoplasmic volume ratio. Early degenerative changes in affected cells always appeared to involve ribosomes. The sensitivity of ganglion cells was attributed to the permeability of ganglionic blood vessels; that of small central nervous system nerve cells may be associated with their low content of protein-synthesizing organelles. 22 references. (Author abstract modified)

003501 Lambert, G. A.; Lang, W. J. Neuropsychopharmacology Research Unit, Department of Psychiatry, New York University Medical Center, 550 First Ave., New York, NY 10016 **Interaction between yohimbine alkaloids and amphetamine in mice.** Psychopharmacology (Berlin). 51(2):209-212, 1977.

The interactions of the yohimbine alkaloids yohimbine, beta-yohimbine and corynanthine with amphetamine were investigated in mice by determining: 1) the toxicity (LD-50) of each alkaloid alone; 2) the LD-50 of each alkaloid in the presence of a constant dose of amphetamine; and 3) the LD-50 of amphetamine in the presence of a constant dose of a yohimbine isomer. Beta yohimbine was approximately twice as toxic as yohimbine, and corynanthine was about one fifth as toxic as yohimbine. There was a mutual potentiation between the toxicities of yohimbine and amphetamine. Potentiation of the toxicity of amphetamine occurred with beta yohimbine, but the effect was not as marked as with yohimbine. Corynanthine antagonized the toxicity of amphetamine. The findings of other investigators regarding the effects of these drugs on catecholaminergic mechanisms in the central nervous system are discussed. It is suggested that the interaction between yohimbine and amphetamine is unlikely to be due to noradrenergic mechanisms but could possibly involve serotoninergic mechanisms or dopaminergic mechanisms. 25 references. (Author abstract modified)

003502 MacDonald, James S.; Harbison, Raymond D. Center in Toxicology, Vanderbilt University Medical Center, Nashville, TN 37232 **Methyl mercury-induced encephalopathy in mice.** Toxicology and Applied Pharmacology. 39(2):195-205, 1977.

An animal model of methyl mercury induced encephalopathy was developed in mice to enable a study of the effects of various newly synthesized chelating agents on methyl mercury toxicity. Administration of methyl mercury to mice via drinking water produced neuropathological and behavioral responses similar to those seen in humans following chronic exposure to organic mercurials. Changes in cellular morphology were seen in the cerebellar cortex of mice exposed to 50 and 10mug of Hg as CH3HgCl per milliliter of drinking water after 8 days of exposure. At this time, posterior paresis began to develop in mice exposed to 50 mug of Hg/ml of drinking water. Histopathological changes were similar in both exposure groups, although paraplegia did not develop in the low dose group until 24 weeks of exposure. Development of overt clinical signs of methyl mercury toxicity correlated well with blood and whole body mercury concentrations. There was a lack of correlation between blood and whole body mercury concentrations and among morphological changes in the cerebellar cortex. 16 references. (Author abstract)

003503 Mikulka, Peter J.; Leard, Barbara; Klein, Stephen B. Psychology Department, Old Dominion University, Norfolk, VA 23508 **Illness-alone exposure as a source of interference with the acquisition and retention of a taste aversion.** Journal of Experimental Psychology: Animal Behavior Processes. 3(2):189-201, 1977.

The effects of exposure to illness alone on acquisition and retention of a taste aversion were studied with 193 rats in four experiments, using unpaired lithium chloride (LiCl) injections as the unconditioned stimulus (US). In Experiment 1, subjects were preexposed to a US; for one group the US was paired with a distinctive taste, whereas for a second group it was not. Then both groups received the US paired with a novel taste. Only the US alone group showed a retardation of subsequent taste aversion conditioning. Experiment 2 indicated that an exposure to LiCl without a specific gustatory cue will interfere with the avoidance of a specific taste, regardless of whether the US experience occurs before or after a single taste/LiCl pairing. Following sucrose/LiCl pairings in Experiment 3A, LiCl alone exposures retroactively interfered with the retention of the prior aversion to sucrose, with the level of post US interference becoming an increasing function of the number of US alone experiences. In Experiment 3B, the association of sucrose with LiCl did not interfere with the development of an almond aversion, whereas LiCl alone exposures following the acquisition of a sucrose aversion proactively interfered with the development of a second taste aversion (almond). It is suggested that a physiological explanation will not adequately account for the results, and they are discussed in the framework of alternative associative models. 31 references. (Author abstract)

003504 Mukhopadhyay, Arun K.; Weisbrodt, Norman. Department of Medicine, Baylor College, Houston, TX 77030 **Effect of dopamine on esophageal motor function.** American Journal of Physiology. 1(1):E19-E24, 1977.

Intravenous administration of dopamine produced a dose dependent decrease in lower esophageal sphincter pressure and a dose dependent increase in contractile activity of the body of the esophagus in opossums. Atropine, phentolamine, propranolol, and bilateral cervical vagotomy did not modify the effect of dopamine. Both haloperidol and bulbocapnine potently antagonized the effect of dopamine. The amplitude of esophageal contraction in the lower esophagus in response to pharyngeal stimulation and esophageal distention was significantly increased after administration of haloperidol. It is concluded that intravenous administration of dopamine has potent effects on the motor function of the lower esophageal sphincter and the body of the esophagus. The effect of dopamine is not mediated via the vagal centers in the brain or cholinergic, muscarinic, and adrenergic receptors. The response of the smooth muscle segment of opossum esophagus to intravenous dopamine is mediated via specific dopamine receptors. The inhibitory dopamine receptors may play a physiological role in controlling the amplitude of esophageal contractions. 18 references. (Author abstract)

003505 Pence, Deborah H.; Miya, Tom S.; Schnell, R. Craig. Department of Pharmacology and Toxicology, School of Pharmacy, Purdue University, West Lafayette, IN 47907 **Cadmium alteration of hexobarbital action: sex-related differences in the rat.** Toxicology and Applied Pharmacology. 39(1):89-96, 1977.

Sex related differences to cadmium alteration of hexobarbital action in the rat were investigated. Three days after ip administration of a single cadmium dose, duration of hexobarbital hypnosis was significantly potentiated in male but not in female rats. Cadmium in larger doses did not alter duration of hexobarbital hypnosis in female rats, although lethality was observed 24 hr after administration of the two higher cadmium doses. Hepatic microsomal metabolism of hexobartital was significantly decreased in male rats but not in females when measured 72 hr after cadmium administration. Addition of cadmium in varying concentrations to microsomes isolated from untreated male and female rats produced a dose dependent inhibition of hexobarbital metabolism at all Cd concentrations in males. In female derived microsomes a significant inhibition of hexobarbital metabolism was observed only at higher cadmium concentrations. These data suggest that a sex related difference exists in the ability of cadmium to alter response to hexobarbital in the rat which appears to be mediated through differences in hepatic microsomal metabolism. 18 references.

003506 Rudy, Jerry W.; Iwens, Judy; Best, Phillip J. Department of Psychology, Green Hall, Princeton University, Princeton, NJ 08540 **Pairing novel exteroceptive cues and illness reduces illness-induced taste aversions.** Journal of Experimental Psychology: Animal Behavior Processes. 3(1):14-25, 1977.

Pairing novel exteroceptive cues with a poison was investigated in rats to determine whether pairing attenuates the development of a taste aversion when sequentially paired with a poison. Four experiments are reported that lead to the conclusion that pairing novel exteroceptive stimulation (placement into a black compartment) with a poison (lithium chloride) attenuates the development of an aversion to a taste (saccharin) subsequently paired with the poison. Such an attenuation effect occurs whether the exteroceptive cues are present or absent when the taste/poison pairing is administered. Interpretation and implications of this finding are discussed. (Journal abstract)

003507 Schreiber, Henry L.; Bell, Robert W.; Kufner, Michael; Villescas, Ramiro. Department of Psychology, Texas Tech University, P.O. Box 4100, Lubbock, TX 79409 **Maternal behavior: a determinant of amphetamine toxicity in rats.** Psychopharmacology (Berlin). 52(2):173-176, 1977.

The effects of maternal behavior in determining d-amphetamine toxicity in rats were studied. At 130 days of age, 31 female rats that had been subjected in infancy to handling, mother separation, both, or neither, were injected with d-amphetamine. The subjects from handled, mother present litters were the only group that showed increased latency to death. This finding indicated that the maternal behavior elicited by early handling, rather than early handling or maternal presence alone, resulted in reduced amphetamine toxicity in the offspring, tested in adulthood. 16 references. (Author abstract modified)

003508 Sklar, Lawrence A.; Amit, Zalman. Center for Research on Drug Dependence, Concordia University, Sir George Williams Campus, Montreal, Quebec, Canada **Effect of aggregation on morphine lethality in rats.** Journal of Pharmacy and Pharmacology (London). 29(2):119-120, 1977.

Three experiments were conducted in rats to assess the role of aggregation in morphine lethality. In the first experiment rats were injected intraperitoneally with 45mg/kg morphine sulphate and isolated in boxes, or aggregated in groups of 6 in large baskets. Twenty of the 24 grouped rats died whereas none of the 24 individually housed died. In the second experiment, a nonlethal dose of morphine was used (15mg/kg) and significantly more of the grouped rats died. In the third experiment rats which had survived an intraperitoneal injection of a high dose of morphine in their home cages died when grouped and injected with a substantially lower dose several days later. Twelve isolated rats were injected with 70mg/kg morphine in their home cages. None of these animals died. One week later 6 of the 12 rats were injected with 45mg/kg morphine in their home cages, while the other 6 rats were grouped in a basket and similarly treated. All of the 6 isolated survived, whereas 5 of the 6 aggregated rats died. The results indicate that grouping morphine injected rats potentiates its lethal effect. It is suggested that, unlike amphetamine, the potentiation of the lethal effects of morphine by aggregation is not caused by a synergism between the stimulant effects of the morphine and the stimulation due to grouping. 7 references.

003509 Snyder, Edward W.; Dustman, Robert E.; Straight, Richard C.; Wayne, Anthony W.; Beck, Edward C. Veterans Administration Hospital and University of Utah, Salt Lake City, UT 84148 **Sudden toxicity of methadone in monkeys: behavioral and electrophysiological evidence.** Pharmacology Biochemistry and Behavior. 6(1):87-92, 1977.

Behavioral and electrophysiological descriptions of the sudden toxicity of methadone along with critical plasma levels of the drug in monkeys was studied. A sudden and potentially lethal toxic reaction to a previously well tolerated maintenance dose of methadone occurred in 4 of 6 monkeys. The reaction was characterized by gross behavioral and respiratory depression and a marked attenuation of both early and late components of the visual evoked response with an increase in most latencies. The nature of the evoked response alteration suggests a widespread central nervous system depressant effect of the drug during toxicity. Concomitant with the toxic reactions were dramatic increases in plasma methadone concentrations. Therefore the observed changes in sensitivity to methadone would appear to be the consequence of a sudden shift in pharmacokinetics resulting in toxic plasma concentrations. 33 references. (Journal abstract modified)

003510 Snyder, Solomon H.; Yamamura, Henry I. Department of Pharmacology, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205 **Antidepressants and the muscarinic acetylocholine receptor.** Archives of General Psychiatry. 34(2):236-239, 1977.

The potency of several tricyclic antidepressants in binding to the muscarinic acetylcholine receptor of rat brain and guinea pig ileum was assessed to determine the tendency of various drugs to elicit atropine-like side effects. These side effects, such as difficult urination and exacerbation of glaucoma symptoms, represent hazards to the elderly individuals who represent the bulk of patients being treated with tricyclic antidepressants. Amitriptyline hydrochloride was found to be about ten times as potent as imipramine hydrochloride, while dimethylate drugs were found to be more potent than monomethylated ones. Because of its greater anticholinergic actions, amitriptyline may not be the drug of choice in patients with prostatic hypertrophy, glaucoma or other conditions where anticholinergic effects would be a liability. Desipramine, the least potent anticholinergic of the drugs studied, might be indicated. 32 references. (Author abstract modified)

003511 Sullivan, F. M.; McElhatton, Patricia R. Dept. of Pharmacology, Guy's Hospital Medical School, London SE1 9RT, England **A comparison of the teratogenic activity of the antiepileptic drugs carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, and primidone in mice.** Toxicology and Applied Pharmacology. 40(2):365-378, 1977.

The teratogenic activity of six commonly used antiepileptic drugs, carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, and primidone, was studied at three dose levels (3, 9 and 18 times the human therapeutic doses) in CD1 mice. The drugs, suspended in 1% carboxymethycellulose, were administered by gastric intubation on Days 6 to 16 of pregnancy, which covers the period from implantation to the end of structural development. The dams were killed 1 day before term and the fetuses were examined. Full length cleft palates were observed in all treated groups with the exception of the clonazepam treated group. This defect was not observed in any of the control groups. Other defects such as exencephaly, enlarged cerebral ventricles, exomphalos, open eyes, undescended tests, abnormal palatal bones other than cleft palate, and fused ribs were seen less frequently. If these results are assessed by ranking the drugs in order of teratogenicity, assessed on either a pooled fetus or a pooled litter basis, the drugs fall into three categories: phenytoin produced the highest incidence of teratogenic effects; carbamazepine, phenobarbital, and primidone produced a lower but still significant incidence of defects; and clonazepam and ethosuximide were the least teratogenic. Nevertheless, there was at least a twofold increase in defects in these latter two treatment groups compared with the controls. 27 references. (Author abstract modified)

003512 Wahlstrom, Goran; Larsson, Roland. Department of Pharmacology, University of Umea, S-901 87 Umea, Sweden **Activity pattern and convulsions in the abstinence period after barbital treatment in the rat.** Pharmacology Biochemistry and Behavior. 6(2):187-192, 1977.

Activity pattern and convulsions were studied in the abstinence (withdrawal) period after barbital treatment in nine rats. Barbital solution was given as the only drinking fluid for 50 days, and activity and convulsive episodes were recorded during treatment and abstinence periods. Sensitivity to hexobarbital was tested with a threshold method. A schedule of 12 hours of light and 12 hours of darkness was used. During treatment, activity started earlier (prior to light off) and ended earlier (prior to light on) than for controls. A clear 24 hr pattern remained and the total activity was the same as in controls. In the first part of the abstinence period activity increased with loss of the 24 hr pattern. Later, activity increased during both light and darkness but a 24 hr pattern influenced by the light/dark cycle was reestablished. Changes in activity seemed to occur in at least two phases and a similar two phase pattern was seen in the changes of the hexobarbital thresholds. The convulsive episodes had several maxima during the abstinence period, and after day 37 no convulsions were seen. It is suggested that all recorded changes can be explained by a common increased excitation in the central nervous system. 19 references. (Author abstract modified)

06 METHODS DEVELOPMENT

003513 Berger, Barry D. Department of Psychology, University of Haifa, Haifa, Israel **An animal model for the measurement and manipulation of problem solving ability.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 187-194).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December 1975, an animal model in which several behavioral measures are tested simultaneously in order to identify whether a drug or other manipulation has a direct or an indirect effect on cognitive function is proposed. Four behavioral measures are made on each trial (i.e. initial error, repetitive errors, latency to initial response, and total time to correct response) of a visual discrimination learning task. It is posited that evaluation of the overall data based on these four measures enables the identification and separation of cognitive performance from associative factors. Two experiments on the effects on learning of parachlorophenylalanine (PCPA), a serotonin (5-hydroxytryptamine) synthesis inhibitor, are presented as examples of the use of this animal model. PCPA facilitated the acquisition of the learning task by a specific effect on the elimination of initial errors. Although there was a tendency for the overall average number of repetitive errors in the PCPA group to be less than that of the vehicle injected controls, no significant differences between the groups were observed using the other behavioral indicators. Other studies have revealed that: 1) the impairment of performance produced by acute administration of chlorpromazine and oxazepam is linked to a general depressant effect of these drugs on performance; 2) facilitation of performance in animals trained under the influence of noncontingent brain stimulation in the medial forebrain bundle is reflected in effects on response latency and total time; and 3) chronic administration of drugs such as chlorpromazine and oxazepam produces a different behavioral profile on learning from that which is found after acute administration of these same agents. 5 references.

003514 Di Leo, Francesco. Maryland Psychiatric Research Center, Box 3235, Baltimore, MD 21228 **The use of psychedelics in psychotherapy.** Journal of Altered States of Consciousness. 2(4):325-337, 1975-76.

The two major ways of using psychedelic drugs in psychotherapy are contrasted. The psycholytic approach using low dose levels, multiple sessions, and setting oriented toward psychoanalytic psychotherapy shows the psychedelics to be powerful tools for intensifying conventional psychodynamic processes. The psychedelic method of using a single large dose

after special preparation of the subject and in a special setting appears to bypass conventional psychodynamics and introduce instead a mystical component in the psychotherapeutic process. Recent work by S. Grof, which identified activation, exteriorization, and integration components in positive and negative experiences or systems of condensed emotional experiences, is applied to the resolution of differences between the two methods. Grof's findings could be applied as a bridge between the Freudian psychodynamic level and the deeper mystical level. It is concluded that unparalleled therapeutic results may occur from combining positive aspects of the psycholytic and psychedelic approaches. Further studies of the psychedelic process with repeated administrations of high doses are recommended. 37 references. (Author abstract modified)

003515 Isaac, W. L.; Isaac, W. Department of Psychology, University of Georgia, Athens, GA 30602 **Differences in placebo effects.** Pharmacology Biochemistry and Behavior. 6(2):235-236, 1977.

The effect on locomotor activity of constant volume injections of bacteriostatic water and bacteriostatic normal saline, two common vehicles for intraperitoneal administration of drugs, was studied in 12 rats. Each substance produced a decrease in activity in addition to the simple effect of administration, and their effects were not equivalent, with water producing a greater decrease than the saline solution. It is suggested that placebo injections of the vehicle used in preparing drug solutions under study be employed in research. Further, the study demonstrates the necessity of adaptation to the injection procedure with the vehicle to be used if such effects are to be eliminated from the outcome of intraperitoneal injections of a drug. 2 references. (Author abstract modified)

003516 Quenzer, L. F.; Gaili, C. L.; Neff, N. H. Laboratory of Preclinical Pharmacology, NIMH, Saint Elizabeth's Hospital, Washington, DC 20032 **Activation of the nigrostriatal dopaminergic pathway by injection of cholera enterotoxin into the substantia nigra.** Science. 195(4273):78-80, 1977.

Twenty four hours after unilateral injection of cholera enterotoxin into the rat substantia nigra there is an increase, in the striatum on the injected side, of basal adenylate cyclase activity, 3,4-dihydroxyphenylacetic acid, and 3-methoxy-4-hydroxyphenylacetic acid. Moreover, there is an increase of motor activity, and rats tend to circle contralateral to the side of the injection. Injection of cholera enterotoxin into brain nuclei may be a useful procedure for pharmacologically activating selected neuronal systems of brain and for studying the pharmacology of drugs that are suspected of interacting with these systems. 14 references. (Author abstract)

003517 Shih, Jean Chen; Rho, Joon. School of Pharmacy, University of Southern California, 1985 Zonal Avenue, Los Angeles, CA 90033 **The specific interaction between LSD and serotonin-binding protein.** Research Communications in Chemical Pathology and Pharmacology. 16(4):637-647, 1977.

The chemical interaction between lysergic acid (LSD) and serotonin binding protein (SBP) by a three dimensional spectroscopic technique is described. This instrument records simultaneously the activation and fluorescence spectra, and plots fluorescence intensity level by a series of isointensity contours. Free LSD exhibits maximum fluorescence at 453nm with excitation maximum at 330nm, while SBP bound LSD shifted its fluorescence and excitation maximum to 465nm and 375nm respectively. These results suggest that the drug/protein interaction caused an extensive delocalization of the molecular orbital electrons and thereby lengthened the electronic conjugation of the drug molecule. Such shift was not observed when LSD was incubated with bovine serum albumin under the same condition. This technique is sensitive and requires a small volume of samples. It permits determination of both free and bound drug in the same sample and provides specific information about the drug and protein interaction. 14 references. (Author abstract modified)

003518 Weinstock, Marta; Speiser, Zipora; Ashkenazi, Ruth. Department of Physiology and Pharmacology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel **Biochemical and pharmacological studies on an animal model of hyperactivity states.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 149-162).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December 1975, biochemical and pharmacological studies using an animal model of hyperactivity states are reported. The effects of inhibition of dopamine (DA) and noradrenalin (NA) synthesis by alpha-methylparatyrosine (AMPT), of selective lesioning of noradrenergic pathways with intraventricular 6-hydroxydopamine (6-OHDA) and of various drugs including diazepam and chlorpromazine, and the selective NA receptor blockers phenoxybenzamine and propranolol on hyperactivity, irritability, and aggression (which are characteristic of hypomania in humans) induced in rats by rearing in isolation were investigated. Isolation reared rats exhibited considerably higher scores for all three behavioral parameters than did group housed controls when open field behavior was observed. AMPT and the 6-OHDA lesions abolished the abnormal hyperactivity in isolation reared animals without affecting normal exploration, suggesting that newly synthesized DA and especially NA, is involved in the mediation of this behavior. Diazepam reduced the hyperactivity of isolated rats but also reduced the normal exploratory activity of controls. Chlorpromazine, in doses too small to affect control animals, modified the abnormal behavior of isolated rats. Both phenoxybenzamine and propranolol reduced the hyperactive behavior of isolated rats to the level of group housed controls. It is suggested that the isolation induced hyperactive syndrome in the rat can serve as a useful model for screening potential psychoactive drugs. It is concluded that isolation induced hyperactivity can be selectively suppressed by drugs which reduce NA activity in doses which do not produce depressant effects in normal animals. 24 references.

CLINICAL PSYCOPHARMACOLOGY

07 EARLY CLINICAL DRUG TRIALS

003519 Charalampous, K. D.; Thornby, John; Ford, B. Kathryn; Freemesser, George F. Department of Psychiatry, Baylor College of Medicine, Texas Medical Center, Houston, TX 77030 **Penfluridol versus oral fluphenazine in the maintenance treatment of chronic schizophrenics.** Current Therapeutic Research. 21(2):215-223, 1977.

Penfluridol, a new oral long-acting antipsychotic, was compared with fluphenazine in the maintenance treatment of chronic schizophrenics. This was a double-blind trial in which patients were stabilized as inpatients on medication and then discharged and followed as outpatients. The total duration of study treatment was 26 weeks. Extrapyramidal side effects were common in both groups. In all measures of both safety and efficacy penfluridol was equal to fluphenazine. It is concluded that penfluridol may provide an improved method of maintenance therapy with fewer relapses, due to increased patient acceptance and improved adherence to prescribed dosage regimens that may be obtained with a long-acting oral preparation. 20 references. (Author abstract modified)

003520 Ehsanullah, Raihana S. B.; Ghose, Karabi; Kirby, Marilyn J.; Turner, P.; Witts, D. Dept. of Clinical Pharmacology, St. Bartholomew's Hospital, London EC1A 7BE, England **Clinical pharmacological studies of tandamine, a potential antidepressive drug.** Psychopharmacology (Berlin). 52(1):73-77, 1977.

Healthy adult volunteers of both sexes were administered tandamine HCl (50mg), desmethylimipramine (DMI) (50mg), or placebo under double-blind conditions to evaluate the physiological and potential antidepressive effects of the drugs. Tandamine, a thiopyranoindole, was more active than DMI in inhibiting the tyramine pressor response after single oral doses. When compared with a placebo, tandamine was found to possess significant anticholinergic activity, to reduce appetite and to produce sedation. Compared with clomipramine, it caused a smaller inhibition of 5-HT but a more marked inhibition of dopamine uptake into human platelets. It is suggested that further clinical and pharmacological studies with tandamine may help to elucidate the respective roles of different monoamines in depression, sedation, and appetite. 11 references. (Author abstract modified)

003521 Ghose, Karabi; Gupta, Ramesh; Coppen, Alec; Lund, Jorgen. Medical Research Council Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey, England **Antidepressant evaluation and the pharmacological actions of FG4963 in depressive patients.** European Journal of Pharmacology (Amsterdam). 42(1):31-37, 1977.

The antidepressant activity and the peripheral autonomic interactions of FG4963, a phenylpiperidine derivative and potent 5-hydroxytryptamine inhibitor at neuronal sites, were tested in 10 patients suffering from primary depressive illness of an endogenous nature and compared to the results obtained with 10 patients treated with amitriptyline. Over a 6 week period FG4963 was significantly inferior to amitriptyline in antidepressant activity. Side-effects were not significantly different between the 2 groups and none were troublesome enough to stop treatment. FG4963 did not appear to be anticholinergic as judged by its lack of effect on salivary flow. Its effect in the dosage used on the tyramine dose pressor response and noradrenaline dose pressor response tests were less than those of amitryptyline. There were no significant correlations between mean plasma FG4963 levels and therapeutic response or dose as expressed as mg/kg body weight. No electrocardiogram abnormalities were observed in the patients on FG4963. 21 references.

003522 Gottschalk, Louis A. Department of Psychiatry and Human Behavior, College of Medicine, University of California, Irvine, CA 92717 **Effects of certain benzodiazepine derivatives on disorganization of thought as manifested in speech.** Current Therapeutic Research. 21(2):192-206, 1977.

Typescripts of tape recorded five minute speech samples were scored blindly for form and content changes in cognitive/intellectual function before and 30 to 300 minutes after the administration of single doses of chlordiazepoxide (25 mg. orally), lorazepam (3mg and 5mg. intramuscularly; and 2mg. and 5mg. intravenously), triazolam (0.25 to 2.0mg. orally), and flurazepam (30mg. orally) and 4 weeks after chronic daily doses of diazepam (15mg. orally/day) and lorazepam (3mg. orally/day). All of the benzodiazepine derivatives, under all conditions and doses, were associated with adverse cognitive effects, the most consistent being significant increases in: a) words or remarks that were not understandable or were inaudible, and b) blocking or incomplete sentences, clauses, or phrases. In the study of the effect of a single oral dose of chlordiazepoxide (25mg.)on cognitive function in 18 chronically anxious patients, more significant increases in the verbal signs of cognitive dysfunction occurred in the 11 patients whose peak chlordiazepoxide blood levels were 0.70 ug./ml. or above. The implications of the temporary adverse cognitive effects accompanying the usual therapeutic mild tranquilizing effects of these drugs are discussed. 24 references. (Author abstract modified)

003523 Pinard, Gilbert. Department of Psychiatry, University of Sherbrooke, Sherbrooke, P.Q., J1H 5N4, Canada **R-806, a tetracyclic antidepressant: an early phase-two study.** Current Therapeutic Research. 21(3):368-373, 1977.

The safety and efficacy of R-806, a tetracyclic antidepressant, were tested in a 31 day, open, early phase trial with ten male hospitalized patients suffering from endogenous depression. Patients were periodically tested on 5 psychological rating scales and underwent electroencephalograms and blood and urine tests during the experiment. Seven patients showed significant improvement according to the 5 rating scales. R-806 did not seem to have anxiolytic properties, and most patients required diazepam as well. Of the few side-effects reported, dry mouth was the most frequent complaint. Further studies on the antidepressant properties of R-806 are recommended. 7 references.

003524 Rafal, Robert D.; Gummow, Linda; Grimm, Robert J. no address **Treatment of progressive supranuclear palsy with methysergide: Neuropsychologic improvement in five patients.** Neurology. 27(4):351, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, neuropsychologic function in five patients with progressive supranuclear palsy was evaluated using electrooculography, videotaped examinations, and psychometric assessment before and after treatment with methysergide. In varying degrees patients exhibited parkinsonian signs,

psychomotor retardation, nuchal dystonia, disturbances of gait and manual praxis, cognitive and affective blunting, pseudobulbar signs, and a supranuclear ophthalmoplegia most severly compromising downward gaze. Oculomotor dysfunction was shown to be but one component of a more global derangement of visuomotor behavior: orienting responses, visual regard, visuosocial expression, and visual tracking and visuopractic skills were impaired. All patients responded favorably to oral methysergide within 1 week. Three enjoyed dramatic improvement affording greater independence and enrichment in the quality of life. They spoke, swallowed, walked, and moved about more easily and demonstrated greater affect and animation. Improvement was witnessed in all measures of attention and visuomotor performance. In two cases where parkinsonian symptoms dominated, methysergide proved a useful adjunct to levodopa/carbidopa. In addition to offering a promising therapy for progressive supranuclear palsy, these observations support the emerging view that midbrain areas of progressive supranuclear palsy involvement are vital to visual perception, the elaboration of visually guided behavior, and the direction of visual attention. (Author abstract)

003525 Stitt, Frank W.; Latour, Roger; Frane, James W. Medical Department, Syntex Laboratory, 3401 Hillview Ave., Palo Alto, CA 94304 **A clinical study of naproxen-disazepam drug interaction on tests of mood and attention.** Current Therapeutic Research. 21(2):149-156, 1977.

A double-blind crossover study was designed to evaluate whether diazepam and naproxen given in combination would produce an effect different from that predicted from each drug given singly on tests of mood and attention; placebo was used as a control. Twenty four healthy volunteers took part in this interaction study. Results showed no significant interaction between these two drugs for four variables: crossout test, positive mood, fatigue, and depression. The remaining two variables, the hidden word test and tension, showed slight differences which were statistically significant but were not considered to be clinically significant. 13 references. (Author abstract modified)

003526 Sukyasyan, A.; Ilsky, E. Clinic of Internal Medicine, Department of Geriatrics, Faculty of Medicine of Cerrahpsa, Istanbul, Turkey **/Effect of piracetam on psychoorganic syndromes of old people./** L'effet du piracetam sur les syndromes psycho-organiques des personnes agees. Revue de Geriatrie (Paris). 2(1):185-187, 1977.

Piracetam (2-pyrrolidone acetamide; Nootropil) was given to 20 senile patients, aged 65 to 97, to test its effect on psychoorganic syndromes of the aged. Changes in behavior were measured by the Benton psychometric test and the Gottfries Cronhom Schalling geriatric score. Statistical differences were noted between the piracetam group and the placebo group with respect to favorable effect on difficulties in verbal expression, short-term memory, emotional incontinence, depression and ideation. Differences between the two groups in terms of symptoms of agitation, forgetfullness, and general physical condition were not statistically significant. It may be concluded that piracetam has an influence on senile psychoorganic syndromes. Piracetam activates the associative mechanism of the brain at an intellectual level, and this is the source of its direct and positive effect on mental functions. 12 references. (Journal abstract modified)

08 DRUG TRIALS IN SCHIZOPHRENIA

003527 Bishop, M. P.; Simpson, George M.; Dunnett, C. W.; Kiltie, Harriet. Lederle Laboratories, Pearl River, NY 10965 **Efficacy of loxapine in the treatment of paranoid schizophrenia.** Psychopharmacology (Berlin). 51(2):107-115, 1977.

Data from 11 controlled studies of loxapine versus chlorpromazine or loxapine versus trifluoperazine in acute schizophrenia or chronic schizophrenia was analyzed. In nonparanoid schizophrenic patients, no statistically significant differences between loxapine and the reference drugs on any of the efficacy variables were found. In paranoid schizophrenic patients, loxapine showed statistically significant superiority over the standard compounds on 20 of 32 relatively independent measures of clinical change, and was marginally superior on 6 of the remaining measures. Findings could not be attributed to inadequate dosages of the reference compounds or to inequality of treatment groups at baseline. 16 references.

003528 Carter, Roy G. Unit 5, Georgia Mental Health Institute, 1256 Briarcliff Rd., N.E., Atlanta, GA 30306 **Psychotolysis with haloperidol: rapid control of the acutely disturbed psychotic patient.** Diseases of the Nervous System. 38(4):237-239, 1977.

Psychotolysis with the neuroleptic agent haloperidol in the rapid control of 48 acutely disturbed psychotic patients is described. The mean duration of psychosis was 9 years; 35 were schizophrenic; 5 had manic-depressive psychoses; 7 had psychoses associated with organic brain syndromes; and 1 had amphetamine psychosis. Response to therapy was measured by comparison of pretreatment and posttreatment severity of four parameters of psychotic mood or thought disorder: 1) psychomotor agitation; 2) hostility and belligerence; 3) auditory hallucinations; and 4) flight of ideas. Within 2 hr of initiation of treatment, severity of all four parameters was reduced significantly. Within 4 hr only 18 patients were disturbed enough to be evaluated for signs and symptoms, but were improved significantly and, for 30 patients, the psychotic episode was over. There was no evidence of a depressive drug effect in any of the patients nor exacerbation of existing depression. Some side-effects were extrapyramidal reactions, especially dystonia or cogwheel rigidity and oculogyric crisis. All responded to treatment with antiparkinsonian agents or resolved spontaneously. Another side-effect was hypotension. 9 references.

003529 Cervantes, P.; Lal, S.; Smith, F.; Guyda, H. Department of Psychiatry, Montreal General Hospital, 1650 Cedar ave., Montreal, Quebec H3G 1A4, Canada **Dopaminergic function in two patients with catalepsy.** Acta Psychiatrica Scandinavica (Kobenhavn). 55(3):214-219, 1977.

Case studies of two schizophrenic patients with catalepsy were reported and dopaminergic function was studied by the administration of apomorphine. In one of these patients the clinical response to apomorphine was compared with that of sodium amytal and the growth hormone response to apomorphine was compared with that of 25 control subjects. Apomorphine had no effect whereas sodium amytal caused rapid disappearance of catatonic symptoms including catalepsy. The peak growth hormone response to apomorphine was similar to that of controls. These data suggest that unlike experimental catalepsy in animals, catalepsy associated with schizophrenia may not be dependent on impaired dopaminergic function. 23 references. (Author abstract modified)

003530 Clark, Mervin L.; Paredes, Alfonso; Costiloe, J. Paul; Fulkerson, F. Grover; Wood, Fredda. Central State Griffin Memorial Hospital, P.O. Box 151, Norman, OK 73070 **Evaluation of two dose levels of loxapine succinate in chronic schizophrenia.** Diseases of the Nervous System. 38(1):7-10, 1977.

An evaluation of two dose levels (100mg. and 50mg.)of loxapine succinate (LOX) was undertaken in a study of 38 chronic schizophrenics in order to establish optimal dose level and treatment duration. In a double-blind placebo controlled design, replicating an earlier study, inpatients were administered 50mg.,100mg.,or a placebo for a 12 week period. Multiple regression analysis ajusting for dose, age, duration of illness, and baseline values indicated that 100mg. LOX was an effective dose as previously shown. In contrast to the previous study, significant response effects were found by the 4th week. In addition, the dose was linearly related to response on nearly all the variables. The principal side-effects were drowsiness and extrapyramidal signs. 11 references. (Author abstract modified)

003531 Cody, John; Robinson, Analee M. High Plains Comprehensive Community Mental Health Center, 208 East Seventh St., Hays, KS 67601 **The effect of low-cost maintenance medication on the rehospitalization of schizophrenic outpatients.** American Journal of Psychiatry. 134(1):73-76, 1977.

To determine whether expense is a relevant factor when schizophrenic outpatients discontinue maintenance medication, low-cost drugs were made available to 44 subjects, while 46 control subjects paid the retail rate. The unexpected results indicate that the group receiving low-cost drugs had a significantly higher rate of rehospitalization. It is suggested that monetary investment on the patient's part may be an important factor in successful drug maintenance. 15 references. (Author abstract)

003532 Cutler, Neal R.; Anderson D. J. no address **A positive response to rapid treatment.** American Journal of Psychiatry. 134(3):329, 1977.

A positive response to rapid pharmacotherapeutic treatment of a patient with a diagnosis of chronic undifferentiated schizophrenia was reported in support of the protocol described by W. H. Anderson and associates (1976). A 38-year-old male with a chronic and long standing history of schizophrenia presented florid psychotic symptoms of conceptual disorganization, hallucinations, delusions, and disorientation to time and place when he was admitted to the hospital. Subsequent to receiving treatment as described by Dr. Anderson and associates (haloperidol intramuscularly every half hour; initial dose of 5mg followed by successive 10mg doses), the patient demonstrated marked improvement on the mental status exam. He was oriented as to time and place and person, denied hallucinations and delusions, and was conceptually reorganized in his thinking. It is recommended that this protocol be used more frequently in the treatment of chronic schizophrenia as well as acute cases. 1 reference.

003533 d'Elia, G.; Jacobsson, L.; von Knorring, L.; Mattsson, B.; Mjorndal, T.; Oreland, L.; Perris, C.; Rapp, W. Department of Psychiatry, Sahlgrens Hospital, S-413 45 Gotenburg, Sweden **Changes in psychopathology in relation to EEG variables and visual averaged evoked responses (V.AER) in schizophrenic patients treated with penfluridol or thiothixene.** Acta Psychiatrica Scandinavica (Kobenhavn). 55(4):309-318, 1977.

Changes in psychopathology in relation to EEG variables and visual averaged evoked response (V.AER) were examined as possible predictors of outcome in clinical psychopharmacology. Twenty eight schizophrenic in patients treated with penfluridol or thiothixene, were followed with clinical ratings with EEG variables, the mean integrated amplitude (MIA) on both the left and right sides, and the within patient variance (WPV) on both sides and with both filters; and with visual V.AER. Determinations of plasma levels of the drugs were also conducted in a search for possible objective measurements of the effects of the treatment, and to try to find measurements that would make it possible to predict the outcome of treatment. MIA left/right and WPV left/right were found to be the most promising variables to follow the effect of treatment. 11 references. (Author abstract)

003534 Donlon, Patrick T.; Swaback, Dwight O.; Osborne, Mary L. University of California at Davis, 2252 45th Street, Sacramento, CA 95817 **Pimozide versus fluphenazine in ambulatory schizophrenics: a 12-month comparison study.** Diseases of the Nervous System. 38(2):119-123, 1977.

Chronic schizophrenic outpatients (N=46) who had been maintained on various neuroleptics for an average of 4 years were abruptly changed to either pimozide (9.6mg per day) or fluphenazine (12.5mg per day) in order to compare the effects of the drugs on long-term management. Previous medication was approximately equivalent to 695mg of chlorpromazine per day. Pimozide and fluphenazine were equally effective in maintaining control of symptomatology of chronic schizophrenics at a level commensurate with or better than that provided by previous medication. Side-effects were characteristic of marketed neuroleptics, similar in severity and occurrence between study drug groups, mainly extrapyramidal symptoms, and readily controlled with antiparkinsonian medication. 17 references. (Author abstract modified)

003535 Ebert, John N.; Ewing, James H.; Rogers, Marsha H.; Reynolds, David J. Crozer Chester Medical Center, 15th and Upland Ave., Upland, Chester, PA 19013 **Changes in primary process expression in hospitalized schizophrenics treated with phenothiazines: two projective tasks compared.** Journal of Genetic Psychology. 130(1):83-94, 1977.

A study of changes in primary process expression in 21 males and 15 females, ages 19-41 years hospitalized schizophrenics treated with phenothiazines is presented with the hypothesis that primary process expression on Gottschlak's Five Minute Verbalization Task (FMV) would be more representative of clinical status in schizophrenia than primary process expression on the Rorschach. The FMV was administered at predrug, 5 weeks, and 13 weeks, and the Rorschach at predrug and 5 weeks. Primary process scoring was according to the Holt system. Clinical improvement was measured by the Lorr Scale and the Burdock Ward Behavior Scale. Over time, Ss produced less primary process on the FMV, while on the Rorschach scores did not change significantly. The scores on the FMV but not on the Rorschach paralleled some measures of clinical improvement. In a factor analysis, scores on the FMV and Rorschach were related to specific but different symptoms. It was concluded that the FMV was more effective in determining clinical improvement, while the Rorschach was perhaps more valuable in assessing the nature of the primary process thinking. 17 references. (Journal abstract modified)

003536 Gardos, George; Cole, Jonathan O. Boston State Hospital Institute of Research and Rehabilitation, 591 Moton

St., Boston, MA 02124 **Weight reduction in sxhizophrenics by molindone.** American Journal of Psychiatry. 134(3):302-304, 1977.

The weight reduction property of molindone, a recently introduced antipsychotic drug of the dihydroindolone class, was evaluated at Boston State Hospital in chronic schizophrenic patients. The subjects were nine severely ill hospitalized chronic schizophrenic patients receiving usual antipsychotic drug therapy, namely chlorpromazine, thioridazine, mesoridazine, fluphenazine, thiothixene, or haloperidol in customary therapeutic dosages. These drugs were replaced with molindone for a period of three months. Results indicated that all nine patients showed weight loss, ranging from .9kg to 16.8kg, with a mean loss of 7.6kg. Most of the loss occurred during the first month. Adverse behavioral change occurred in one female patient who was removed from the program. Periodic agitation was noted in one other patient. Two patients claimed a euphoric reaction. In the remaining five patients, there was no apparent behavioral change. It is concluded that the behavioral changes were unremarkable and that the mechanism producing the weight loss is uncertain, but a central anorexigenic effect may be an important factor, especially with regard to obese schizophrenic patients. 11 references.

003537 Gerlach, J.; Rasmussen, P. T.; Hansen, L.; Kristjansen, P. Rigshospitalet 9, Blegdamsvej, DK-2100 Kobenhavn, Denmark **Antiparkinsonian agents and long-term neuroleptic treatment: effect of G 31.406, orphenadrine and placebo on parkinsonism, schizophrenic symptoms, depression and anxiety.** Acta Psychiatrica Scandinavica (Kobenhavn). 55(4):251-260, 1977.

The need for medication with anticholinergic antiparkinsonian drugs was examined in 118 schizophrenic patients under long-term neuroleptic treatment. It was found that: 1) none of 18 patients under treatment with low mg potency neuroleptics (chlorprothixene, clozapine, and thioridazine) had any need for anticholinergics; 2) of 60 patients under treatment with short acting high mg potency neuroleptics (perphenazine less than 16 mg daily and haloperidol less than 2 mg daily) nine patients (15%) required medication with anticholinergics; whereas 3) of 40 patients under treatment with long acting (depot) neuroleptics, 17 (43%) had a need for anticholinergic medication; and 4) no patient factors predisposing to the need for continued antiparkinsonian treatment could be identified. In an additional double-blind cross-over study of 12 patients presenting persisting neuroleptic induced parkinsonism, it was found that G 31.406 (a new potenitally antiparkinsonian drug), compared with placebo, had an anitparkinsonian effect as well as an antidepressant effect. G 31.406 resulted in an improvement in anxiety and schizophrenia score in some patients. Compared with placebo, orphenadrine had a more questionable effect on parkinsonism and no significant effect on mental symptoms. There were no significant differences between the effects of G 31.406 and orphenadrine. 31 references. (Author abstract)

003538 Gillis, John S.; Davis, Harry G. Oregon State University, Corvallis, OR **The effects of thioridazine and mesoridazine on the interpersonal learning of acute schizophrenics.** Current Therapeutic Research. 21(4):507-517, 1977.

Following a 4 week, drug free period, 16 newly hospitalized acute schizophrenics received either thioridazine concentrate or mesoridazine as the besylate concentrate. Starting dose level for thioridazine was 50 to 100mg, t.i.d.,and for mesoridazine, 25 to 50mg, t.i.d.,dose levels thereafter being determined by patients' clinical response. After 8 weeks on these regimens, subjects completed a series of structured tasks designed to assess their abilities to learn from social interactions. Thioridazine subjects were superior to those receiving mesoridazine on each of the performance indices derived from these tasks. These group differences reached significance on the measure of cognitive control, an index of the patient's ability to maintain a stable approach to cognitive tasks. Implications for the chemotherapy of schizophrenia are considered. 21 references. (Author abstract)

003539 Goldberg, Solomon C.; Schooler, Nina R.; Hogarty, Gerard E.; Roper, Margaret. Psychopharmacology Research Branch, National Institute of Mental Health, 5600 Fishers Lane, Rockville, MD 20852 **Prediction of relapse in schizophrenic outpatients treated by drug and sociotherapy.** Archives of General Psychiatry. 34(2):171-184, 1977.

To test the theory that schizophrenic patients with good prognostic signs will do well without neuroleptic drug treatment, and to assess the effectiveness of a sociotherapy called major role therapy (MRT) in forestalling relapse, 354 newly discharged schizophrenics were grouped into four treatment categories and a double-blind study of their outpatient records was conducted. The four groups were chlorpromazine and MRT, clorpromazine alone, placebo and MRT, and placebo and no MRT. Contrary to prediction, patients with good prognostic signs profited the most from drug treatment. Patients who benefitted little were men: 1) whose families were disrupted earlier in their lives; 2) who lived alone or with extended families whose attitudes toward the study were not positive; and 3) who were irregular in taking their medication. It is concluded that the drug nonresponders can be helped by ensuring regularity of drug therapy. MRT, a combination of social casework and vocational rehabilitation, was shown to forestall relapse in a disordinal manner. Asymptomatic patients benefitted from MRT, while it hastened relapse in patients with greater symptom severity. It is posited that because MRT may induce a state with which the patient cannot cope, such therapy should be deferred until the patient is essentially asymptomatic. 17 references. (Author abstract modified)

003540 Gruzelier, John; Hammond, Nick. Neuropsychology Unit, Friern Hospital, University College Hospital Medical School, University of London, London, England **The effect of chlorpromazine upon bilateral asymmetries in bioelectrical skin reactivity of schizophrenics.** Studia Psychologica (Bratislava). 19(1):40-51, 1977.

Bilateral electrodermal orienting activity was recorded from 19 chronic schizophrenics while on chlorpromazine, on placebo, and again on chlorpromazine. As found previously, about half of the schizophrenics exhibited no orienting responses; in all three conditions. The findings of bilateral asymmetries in both the amplitude and number of responses were replicated: -- the majority showed higher right hand response amplitudes and there were instances of unilateral nonresponding of the left hand. Chlorpromazine reduced bilateral asymmetries in skin conductance levels and may interact with adaptation effects to weaken lateral dominance in response amplitudes. A shift in bilateral asymmetries on chlorpromazine has been found with other measures and this may underlie its therapeutic efficacy. 45 references. (Author abstract)

003541 Hogarty, Gerard E.; Ulrich, Richard F. Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15261 **Temporal effects of drug and placebo in delaying relapse in schizophrenic outpatients.** Archives of General Psychiatry. 34(3):297-301, 1977.

In a double-blind study of the temporal effects of drug and placebo in delaying relapse in schizophrenic outpatients, 374 schizophrenic subjects were randomly assigned to chlorpromazine or placebo therapy following a 2 month period of drug stabilization postdischarge. Because the potential for unwanted side-effects, particularly tardive dyskinesia, following long-term aftercare maintenance with antipsychotic medication has led to questioning its continued use for schizophrenics, the study examined whether the risk of relapse declines with time and if so whether the advantage of drug therapy justifies continued use beyond 1 or 2 years. Results derived by analysis of variance indicated that while the risk of relapse does decline substantially, it remains twice as high for placebo treated patients as drug treated patients even after 2 years of treatment. The prophylactic effect of maintenance chemotherapy appears to be one to two times larger than generally estimated by the less precise cumulative percentage method. 24 references. (Author abstract modified)

003542 James, Norman McI.; Montague, Anne F. Ashburn Hall Private Psychiatric Hospital, Dunedin, New Zealand **Penfluridol: a double blind trial in chronic schizophrenia.** New Zealand Medical Journal (Dunedin). 85(580):53-54, 1977.

The effects of oral penfluridol given weekly were compared with the effects of monthly injections of fluphenazine decanoate in a small group of chronic schizophrenic patients. Sixteen chronic schizophrenic inpatients between the ages of 20 and 55 were randomly assigned to each drug group for the 24 week trial. Double-blindness was achieved by giving monthly saline injections to those on penfluridol tablets, and weekly placebo tablets to those receiving fluphenazine decanoate injections. Patient maintenance on weekly doses of penfluridol was found to be as effective as on monthly injections of fluphenazine decanoate. 7 references. (Author abstract modified)

003543 Kety, Seymour S. Harvard Medical School, Massachusetts General Hospital, Boston, MA 02114 **The biological substrates of schizophrenia.** In: Research on disorders of the mind: progress and prospects. Rockville, MD, NIMH, 1977. 54 p. (p. 2-6) $1.20.

A brief review indicative of the various areas of research subsumed under the heading of biological substrates of schizophrenia is presented in this condensation of a paper presented at the 100th meeting of the National Advisory Mental Health Council held September, 1975, on Research on Disorders of the Mind. Early research on oxygen consumption of the brain, epinephrine metabolism, and genetics as related to schizophrenia, are recounted and provided as blind alleys in the history of schizophrenia research. Currently tenable research approaches to the biological substrates of schizophrenia are noted, and the assurance that fundamental biological research will provide more effective means for prevention and treatment, is given.

003544 Kingstone, E.; Grof, P.; Furlong, W.; Jacques, W.; Virc, L.; Daigle, L. Department of Psychiatry, Sunnybrook Medical Centre, University of Toronto, Toronto, Ontario, Canada **Penfluridol, a peroral long-acting neuroleptic, for the maintenance treatment of schizophrenic patients who relapse.** Journal of Clinical Pharmacology. 17(4):252-258, 1977.

The efficacy of penfluridol, a long-acting neuroleptic, for the maintenance treatment of schizophrenic patients who relapse was studied in 20 males and 8 females in 3 hospitals over a 16 wk period. All the patients selected had a history of schizophrenia and a new admission within a month prior to the study. They were stabilized with use of a conventional neuroleptic, usually chlorpromazine, which was withdrawn during the first week of study. Patients were given 1 to 3 20mg tablets of penfluridol weekly. Subjects were tested before starting and weekly during the test, using the Brief Psychiatric Rating Scale (BPRS) and the Katz Adjustment Scale (KAS). A series of 12 metabolic tests, complete blood count, urinalysis, blood pressure, weight, pulse, and temperature were monitored at regular intervals. The psychological tests showed statistical improvement over the 16 wk period. Pulse rate decreased and weight increased slightly, signs of general overall improvement, and no serious side-effects occurred. The major side-effect was restlessness, and this decreased in incidence as the test proceeded. A statistically significant increase in blood urea nitrogen occurred, but the significance of this was not clear. It was felt that the low dosage schedule and elimination of the needle, as was necessary with previously used medications, was a factor in patient acceptability. 12 references.

003545 Klerman, Gerald. Harvard Medical School, Massachusetts General Hospital, Boston, MA 12114 **Analysis of the impact of phenothiazines and related drugs on the treatment of schizophrenia.** In: Research on disorders of the mind: progress and prospects. Rockville, MD, NIMH, 1977. 54 p. (p. 20-21) $1.20.

A condensation of a paper presented at the 100th meeting of the National Advisory Mental Health Council held September, 1975, on Research on Disorders of the Mind analyzes the impact of phenothiazines and related drugs on the treatment of schizophrenia. The implications of the fact that the phenothiazines and related drugs act to reduce the symptoms of schizophrenia are noted, and the chief one of these (the reduction in number of hospitalized psychotic patients) is discussed. More psychotic patients are being treated in general hospitals than previously, and more psychotic patients are being treated on an outpatient basis. Side-effects of prolonged phenothiazine treatment and popular reactions against the treatment of psychotic patients in the community are discussed.

003546 Lindstrom, L. H.; Gunne, L.-M.; Ost, L.-G.; Persson, E. Psychiatric Research Center, University of Uppsala, Ullerakers Hospital, S-75017 uppsala, Sweden **Thyrotropin-releasing hormone (TRH) in chronic schizophrenia: a controlled study.** Acta Psychiatrica Scandinavica (Kobenhaven). 55(1):74-80, 1977.

A controlled study on the effect of synthetic Thyrotropin Releasing Hormone (TRH) versus placebo in 10 drug free chronic schizophrenics is presented. TRH 600 microgram or placebo was administered intravenously on 4 consecutive days in a double-blind crossover design and the schizophrenic symptoms were scored daily by use of two rating scales. Blood samples were taken before and 30 and 45 minutes after the first and the fourth injection and analyzed for TSH. No changes in symptom intensity were found during the TRH or placebo treatment period and no difference was obtained between the two treatments. The dose of TRH used caused a significant increase in the plasma level of TSH which indicated a normal pituitary responsiveness to TRH. The data do not support the notion that TRH has a beneficial effect in chronic schizophrenic patients. 12 references. (Author abstract)

003547 Rifkin, Arthur; Quitkin, Frederic; Kane, John; Klein, Donald F. Department of Psychiatry, Long Island Jewish-Hillside Medical Center, Glen Oaks, NY 11004 **Fluphenazine decanoate, oral fluphenazine, and placebo in the treatment of**

remitted schizophrenics. II. Rating scale data. Psychopharmacology Bulletin. 13(2):49-50, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, rating scale data were used to evaluate fluphenazine decanoate (FD), oral fluphenazine (F) and placebo (P) in the treatment of remitted schizophrenics in a double-blind study for 1 year. Relapse rate was 15/22 P patients (68%) compared to 10% in the F and FD groups. Fifteen percent of all patients were terminated because of drug toxicity; of these, 73% received FD and manifested akinesia. Thirty five percent of all FD patients were terminated because of akinesia, defined as diminished behavioral spontaneity as well as gross motor change. The baseline raing scales showed no differences between the three treatment groups. On the Clinical Global Impressions scale, the terminators did not show any worsening, indicating they were not mislabeled as clinical relapses. Patients terminated for relapse showed significant worsening on the Brief Psychiatric Rating Scale (BRPS) items which supported the clinical diagnosis of relapse. Four out of five items from the BRPS that would reflect akinesia and 3 out of 4 items on the Periodic Evaluation Record-Community scale showed worsening at termination for the FD patients. The results support the clinical findings that there are more schizophrenic relapses on placebo, and patients on fluphenazine decanoate (FD) have a high incidence of akinesia. 2 references.

003548 Thorup, M.; Fog, R. St. Hans Hospital, Department E., DK-4000 Roskilde, Denmark **Clozapine treatment of schizophrenic patients: plasma concentration and coagulation factors.** Acta Psychiatrica Scandinavica (Stockholm). 55(2):123-126, 1977.

The plasma concentration and coagulation factors were studied for a minimum of 12 weeks in 11 hospitalized male chronic schizophrenics receiving clozapine as their only neuroleptic medication. Wide variations in the plasma concentration of clozapine were found in different patients who received the same oral dose, as well as great changes from week to week in the individual patient given a constant dose. The plasma levels of clozapine appeared to have no correlation with either the clinical effect or the side-effects. No differences with regard to coagulation factors were found between the patients and the controls. 13 references. (Journal abstract)

09 DRUG TRIALS IN AFFECTIVE DISORDERS

003549 Ansoms, C.; De Backer-Dierick, G.; Vereecken, J. L. T. M. Psychiatric Institute of the Alexian Brothers, Veldbornstraat 39, B-3300 Tienen, Belgium **Sleep disorders in patients with severe mental depression: double-blind placebo-controlled evaluation of the value of pipamperone (Dipiperon).** Acta Psychiatrica Scandinavica (Stockholm). 55(2):116-122, 1977.

Pipamperone was compared double-blindly with placebo to evaluate its capacity to relieve sleep disorders in 40 depressive inpatients. At the end of the 1 week trial, most of the items relating to sleep disturbances had improved significantly in the 24 patients of the pipamperone group whereas only a few items showed such a change in the control group. On the Hamilton depression scale, improvement in the pipamperone patients was also superior to that in the placebo group as regards the items "depressed mood" and "insight." 19 references. (Journal abstract)

003550 Buchsbaum, Monte S.; Van Kammen, Daniel P.; Murphy, Dennis L. Adult Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20014 **Individual differences in average evoked responses to d- and l-amphetamine with and without lithium carbonate in depressed patients.** Psychopharmacology (Berlin). 51(2):129-135, 1977.

Visual average evoked responses (AERs) to four intensities of light were studied in hospitalized depressed patients after administration of placebo, dextroamphetamine, levoamphetamine, lithium, and dextroamphetamine or levoamphetamine combined with lithium. The subjective effects of the drugs were assessed by a mood and behavior self-rating scale completed by the patients. The amphetamines produced only minor AER changes which were attenuated by coadministration of lithium. Patients who had larger AER amplitudes on baseline also tended to have larger increases in activation ratings and reductions in depression ratings. The amount of increase in AER amplitude or amplitude/intensity slope with amphetamine was also significantly correlated with the amount of increase in activation or euphoria ratings with amphetamine administration. These effects were most prominent in the same P100 component that previously have been found to differentiate bipolar depressed and unipolar depressed patient groups. 48 references. (Author abstract modified)

003551 Burns, David; Mendels, Joseph. Foundations' Fund for Research in Psychiatry, University of Pennsylvania, Philadelphia, PA 19174 **Biogenic amine precursors and affective illnesses.** In: Fann, W., Phenomenology and treatment of depression. New York, Spectrum, 1977. 350 p. (p. 33-67).

In a paper presented to a symposium on Phenomenology and Treatment of Depression held at Baylor University in December, 1975, the results of studies testing the effectiveness of biogenic amine precursors in depression are reviewed. These conclusions are reached: 1) L-dopa is not a clinically effective antidepressant; however, inasmuch as L-dopa administration may not have a significant effect on CNS norepinephrine turnover, this finding does not have significant implications for the hypothesis that decreased brain noradrenergic activity exists in some depressed patients; 2) there is no conclusive evidence that tryptophan and 5-hydroxytryptophan have a significant antidepressant effect in unipolar patients; however, there is evidence that L-tryptophan potentiates the antidepressant effects of monoamine oxidase inhibitors; 3) reports that L-tryptophan has antimanic and antidepressant effects in bipolar patients and evidence that L-tryptophan and lithium may have similar effects on CNS serotonergic systems are consistent with the hypothesis of abnormalities of central serotonergic activity in both mania and depression. 133 references.

003552 Burrows, Graham D.; Maguire, Kay P.; Scoggins, Bruce A.; Stevenson, James; Davies, Brian. Department of Psychiatry, Royal Melbourne Hospital, Melbourne, Victoria 3050, Australia **Plasma nortriptyline and clinical response -- a study using changing plasma levels.** Psychological Medicine (London). 7(1):87-91, 1977.

The effect of changes in plasma levels of nortriptyline on changes in patients' severity of depression was studied. In a 5-week study of 22 depressed patients treated with nortriptyline, significant changes in plasma levels, both elevated and reduced, were deliberately produced in the third and fourth weeks of each patient's treatment. Correlation of plasma nortriptyline levels and changes in the severity of depression, as measured by the Hamilton Depression Scale, showed no sig-

nificant relationships. The implications of the study are discussed. 17 references. (Author abstract modified)

003553 Chouinard, G.; Young, S. N.; Annable, L.; Sourkes, T. L. Department of Psychiatry, McGill University, Montreal, Quebec, Canada **Tryptophan-nicotinamide combination in depression.** Lancet (London). No. 8005:249, 1977.

In a letter to the editor tryptophan/nicotinamide combination was tested in 11 depressed patients with diagnosis of primary affective disorder, and results are discussed in terms of rating scale measures and plasma tryptophan concentrations. Patients receiving a tryptophan/nicotinamide combination showed statistically significant improvement in mean total scores on both the Hamilton psychiatric rating scale for depression and the Beck depression inventory, and there was an appreciable, although not statistically significant, correlation between the increase in total plasma tryptophan concentration and score improvement. Nictotinamide reduces breakdown of tryptophan in the liver, and it is suggested that the relationship between clinical response and the rise in plasma tryptophan supports the thesis that the relative ineffectiveness of tryptophan in the past has been due to its high rate of catabolism in the liver. 7 references. (Author abstract modified)

003554 Comfort, Alex. 683 Oak Grove Drive, Santa Barbara, CA 93108 **Morphine as antipsychotic drug.** Lancet (London). No. 8002:95, 1977.

In a letter to the editor, observations are presented on the antipsychotic possibilities of morphine addiction. It is suggested that there may be a group of people who do rely on morphinoid drugs as primary suppressants of intolerable prepsychotic sensations, and that these are the addicts who fail to display enough motivation to undertake the physical distress of withdrawal. The possibility of an alternative approach to addiction is raised. It is also felt that for some psychotics, morphinoids may be the only effective antipsychotic drug, despite the drug's other risks. Older experience with stabilized and supervised addicts is seen as confirming this observation.

003555 d'Elia, G.; Borg, S.; Hermann, L.; Lundin, G.; Perris, C.; Raotma, H.; Roman, G.; Siwers, B. Psychiatric Clinic, Sahlgrens Hospital, S-413 45 Gothenburg, Sweden **Comparative clinical evaluation of lofepramine and imipramine: psychiatric aspects.** Acta Psychiatrica Scandinavica (Kobenhavn). 55(1):10-20, 1977.

Lofepramine, an imipramine analogue, was compared with imipramine in a multicenter, double-blind clinical trial. The 62 patients had a depressive syndrome that normally would have been treated with a tricyclic antidepressant. These patients had not received any adequate treatment for their present depressive episode. After a washout period and once a week during treatment, routine laboratory tests and electrocardiograms were done. Depression ratings with the Cronholm-Ottosson depression rating scale were performed. In the 5th week of treatment 15 out of 31 in the lofepramine group and 18 out of 31 in the imipramine group had recovered. This difference was not significant, nor did the median values of individual symptoms differ between the groups. The side-effects were moderate and the two groups only differed significantly in the dry mouth items and accommodation disturbances in favor of lofepramine. The drug compliance was checked by plasma levels of desmethylimipramine in the imipramine group, parent compound, and apparent desmethylimipramine in the lofepramine group. The clinical outcome in the two groups did not differ significantly; interpretation of this result is discussed in relation to the reliability of rating and selection of patients. 14 references. (Author abstract)

003556 Fann, William E.; Wheless, Jeanine C. Baylor College of Medicine, Houston, TX 77030 **Pharmacological treatment of the moderately anxious and depressed patient.** In: Fann, W., Phenomenology and treatment of depression. New York, Spectrum, 1977. 350 p. (p. 273-283).

In a paper presented to a symposium on Phenomenology and Treatment of Depression held at Baylor University in December, 1975, some of the available data regarding mixed anxiety/depression are reviewed and presented in a form thought to be useful to clinicians faced with problems of differentiating diagnoses and prescribing proper pharmacotherapy. The anxious/depressed subtype is discussed generally, and the question of whether to use active medication or placebo is considered. Various rating scales for anxiety/depression are noted briefly, and published research on the treatment of anxious/depressed patients is reviewed. General guidelines are presented for the clinician in outpatient practice treating patients with mixed anxiety/depression. 14 references.

003557 Forrest, W. A. CIBA Laboratories, Horsham, West Sussex, England **Maprotiline (Ludiomil) in depression: a report of a monitored release study of 10,000 patients in general practice.** Journal of International Medical Research (Northampton). 5(1):42-47, 1977.

In order to determine the efficacy, tolerance, and patient and physician acceptability of maprotiline following initial marketing of the drug, general practitioners were asked to complete record forms for patients treated for depression with this drug. Data presented were based on the first 10,000 patient record forms returned which satisfied protocol criteria. It was found that a single dose of matprotiline 75mg at night was effective therapy in three quarters of the patients who completed the study. At this dose the drug was well tolerated, and troublesome side-effects presented in only a small percentage of patients. Drowsiness was the most commonly reported side-effect, and the main reason for withdrawal of treatment. The drug was acceptable to most physicians, and in this study was used in a wide range of patients and over a broad spectrum of depressive illness. 16 references. (Author abstract modified)

003558 Frazer, Alan. Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104 **Adrenergic responses in the affective disorders.** In: Brady, J., Psychiatry: areas of promise and advancement. New York, Spectrum, 1977. 253 p. (p. 43-52).

In view of the dearth of investigations measuring amine or amine precursor induced responses in depression, two investigations of catecholaminergic responses in drug free male depressives were undertaken. In experiment one, the stimulation produced by prostaglandin E1 and the inhibition produced by norepinephrine on the net synthesis of adenosine 3',5'-monophosphate (cyclic-AMP) in platelets, obtained from normal and depressed subjects, incubated in vitro was measured. No differences between the patient and control groups was found. In experiment two, growth hormone (GH) response to apomorphine and to L-DOPA was measured in 13 depressed subjects. Results suggest a trend for more inadequate responses to L-DOPA than to apomorphine in the depressed or hypomanic subjects. Comparison with the resuls of an earlier study of GH response to L-DOPA in normal subjects, however, indicates only slight differences between normal and depressed subject responses. Results of these studies do not support the idea of a generalized amine receptor or response abnormality in depression. Further research is suggested. 19 references.

003559 Gershon, Samuel. Neuropsychopharmacology Research Unit, New York University Medical Center., New York, NY 10016 **The impact of lithium on the treatment of manic-depressive disorders.** In: Research on disorders of the mind: progress and prospects. Rockville, MD, NIMH, 1977. 54 p. (p. 22-23) $1.20.

A condensation of a paper presented at the 100th meeting of the National Advisory Mental Health Council held September, 1975, on Research on Disorders of the Mind discusses the impact of lithium on the treatment of manic-depressive disorders. The history of lithium therapy for affective disorders is recounted, and it is claimed that lithium therapy has no significant side-effects. The work with lithium and recurrent disorders suggests that some psychoactive drugs can be effective in prevention as well as treatment of psychotic episodes. Posttraumatic depression and depression in the aged are mentioned as two types of depression which are rarely treated effectively with drugs.

003560 Glassman, Alexander H.; Perel, James M.; Shostak, Michael; Kantor, Shepard J.; Fleiss, Joseph L. New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032 **Clinical implications of imipramine plasma levels for depressive illness.** Archives of General Psychiatry. 34(2):197-204, 1977.

Following one drug free week and one week of placebo, 60 depressed nonschizophrenic patients received imipramine hydrochloride for 28 days to determine the relationship between the plasma steady state variability of antidepressant drugs and clinical outcome. Plasma levels of imipramine and its metabolite desipramine hydrochloride (desmethylimipramine) were measured three times weekly. Steadystate levels ranged from 50 to 1050ng/ml. There was a statistically and clinically significant relationship between plasma levels and response which existed across the entire sample and was accentuated when the bipolar and unipolar nondelusional populations were examined. Because a strong relationship between sex and outcome was observed, the unipolar nondelusional patients were stratified by sex and a significant relationship still persisted. Only the unipolar delusional patients failed to demonstrate an association between blood level and clinical response. 34 references. (Author abstract modified)

003561 Heninger, George R.; Kirstein, Larry. Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519 **Effects of lithium carbonate on motor activity in mania and depression.** Journal of Nervous and Mental Disease. 164(3):168-175, 1977.

A telemetered movement recording system and nursing ratings of behavior were utilized to assess spontaneous motor activity and symptom intensity of 15 patients with affective illness before and during lithium carbonate treatment. Prior to treatment patients rated hyperactive/elated, angry, and agitated had more motor activity, and patients rated anergic and retarded had less motor activity. Lithium carbonate treatment was not associated with any uniform change in motor activity for all patients; however, patients with a decrease during treatment in thought disorder, motor agitation, and hyperactivity/elation had a decrease in motor activity, and patients who had a decrease in depressed mood, anergia, motor retardation, and social withdrawal had an increase in motor activity. The data indicate that lithium does not exert a strong and consistent direct effect on spontaneous motor movement, and that when changes in movement do occur, they relate to changes in clinical states. 30 references. (Author abstract modified)

003562 Hullin, R. P. Metabolic Research Unit, High Royds Hospital, Ilkley, Yorkshire, England **Biochemistry of the affective disorders.** Journal of International Medical Research (Northampton). 5(Supplement 1): 140-145, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the idea that affective illness might be due to some biochemical malfunction is examined. A number of features of affective illness lend support to the biological hypothesis of etiology. The evidence is briefly reviewed. There are three principal areas of biochemical interest in depression; electrolytes, biogenic amines, and neuroendocrine abnormalities. Each of these is briefly reviewed from a biochemical and physiological point of view and the psychopharmacological treatment regimen for each area outlined. (Journal abstract modified)

003563 Karacan, Ismet; Williams, Robert L.; Salis, Patricia J. Baylor College of Medicine, Houston, TX 77030 **Sleep and sleep abnormalities in depression.** In: Fann, W., Phenomenology and treatment of depression. New York, Spectrum, 1977. 350 p. (p. 167-186).

In a paper presented to a symposium on Phenomenology and Treatment of Depression held at Baylor University in December, 1975, sleep electroencephalographic/ electrooculographic studies among depressed patients and antidepressant effects on sleep patterns are reviewed briefly, and the results of one laboratory study using an antidepressant are presented. The effects of several major antidepressants (amitryptyline, desipramine, imipramine, and lithium) on sleep patterns are examined. Doxepin, a tricyclic agent, was tried among 11 male and female neurotic depressives whose illnesses had durations of 2 months to 14 years. The study showed clearly that the sleep electroencephalographic/electrooculographic patterns, subjective ratings of sleep quality and quantity, and patient and physician ratings of mood and clinical status were improved by doxepin therapy. 47 references.

003564 Magnus, R. V.; Schiff, A. A. Rubery Hill Hospital, Rubery, Birmingham, England **Once-daily treatment for mixed anxiety/depressive states: a comparison of slow release amitriptyline and fluphenazine with nortriptyline.** Journal of International Medical Research (Northampton). 5(2):109-113, 1977.

Patients suffering from mixed anxiety/depressive states referred to a psychiatric outpatient clinic completed a 4 week course of either a once daily tablet of 30mg nortriptyline with 1.5mg fluphenazine, or a sustained release capsule of 50mg amitriptyline once daily, on a double-blind basis. Depression improved satisfactorily on either treatment, but there was a greater reduction of anxiety on fluphenazine/nortriptyline. Drowsiness, however, occurred more frequently among the patients on amitriptyline, suggesting the sedative properties of this drug did not substitute adequately for a specific anxiolytic effect. Dry mouth was also noticeably more frequent with amitriptyline. The results suggest that the sustained release characteristics of the amitriptyline preparation lead to a maximization of side-effects during the day without conferring any therapeutic advantage. 13 references. (Author abstract modified)

003565 McCabe, Michael S.; Norris, Barbara. Department of Psychiatry, University of Iowa, Iowa City, IA **ECT versus chlorpromazine in mania.** Biological Psychiatry. 12(2):245-254, 1977.

A comparison of therapeutic efficacy of electroconvulsive therapy (ECT), chlorpromazine therapy, and no active treatment in mania is presented. Twenty eight control patients diag-

nosed as manic were selected from consecutive admissions to the University of Iowa Psychiatric Hospital in the period 1935-1941 when there was no active treatment given. Twenty eight patients treated with ECT were selected from the period 1945 to 1949, and 28 chlorpromazine treated patients were selected from the period 1958 to 1964. Symptoms sufficient to fulfill a research diagnosis of mania had to be documented in the record for all patients. Results compare symptomatology, duration of hospital admission, discharge condition, discharge category, social recovery, and followup. Both ECT and chlorpromazine were superior to no active treatment for outcome measures considered. Ten chlorpromazine treated patients did not respond satisfactorily to the chlorpromazine treatment but recovered with ECT treatment. 17 references. (Author abstract modified)

003566 Mendels, J.; Schless, A. P. V. A. Hospital, 151 E., Philadelphia, PA 19104 **Antidepressant effects of desipramine administered in two dosage schedules.** Diseases of the Nervous System. 38(4):249-251, 1977.

The antidepressant effects of desipramine when given in 50mg doses three times a day (14 patients) and in a single bedtime dose of 150mg (20 patients) were compared in moderately to markedly depressed outpatients in a double-blind study. The overwhelming majority had bipolar depression. Both patients showed significant reduction in depression with no significant differences between the groups. There were few changes in sleep patterns with no differences between the groups. Side-effects most frequently reported were dry mouth, dizziness, headache, and insomnia. There were no significant differences between the groups in type or severity of adverse effects, although the percentage of adverse effects was generally higher in the divided dose group than in the single dose group; however, there were fewer dropouts from the single dose group, suggesting less troublesome side-effects. 8 references.

003567 Mendels, Joe. Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104 **Psychobiology of depression.** In: Brady, J., Psychiatry: areas of promise and advancement. New York, Spectrum, 1977. 253 p. (p. 35-42).

Psychobiological approaches to the study of depression are discussed with an emphasis on recent research aimed at characterizing a lithium carbonate responsive subgroup of depressive patients. It is suggested that the study of clinical manifestations of depression requires an heterogenous approach that includes investigation of neurotransmitter balances, endocrine functions, and electrolyte metabolism. A series of investigations indicate that the lithium responsive depressed patient tends to be characterized by: a bipolar history; and endogenous symptom profile; a proportionately higher concentration of intracellular lithium; an increased averaged evoked response; elevated pretreatment plasma calcium/magnesium ratio; and reduced concentrations of 5-hydroxyindoleacetic acid in the lumbar spinal fluid. Further preliminary studies have indicated that lithium responsive patients also have a higher erythrocyte lithium/plasma lithium ratio, higher baseline erythrocyte sodium concentrations, and lower active sodium transport which may be the result of genetically determined differences in cell membrane properties regulating electrolyte distribution. 22 references.

003568 Mendlewicz, J.; Verbanck, P.; Brunswick, D.; Frazer, A.; Mendels, J.; Gottlieb, J. Institute of Psychiatry, Brugmann Hospital, Free University of Brussels, B-1020 Brussels, Belgium **Lithium ratio and clinical response in manic-depressive illness.** Lancet (London). No.8001:41-42, 1977.

In letters to the editor, three different studies concerning the effect of lithium (Li) on manic-depressive patients are reported. In the first study the Li ratio and long-term response to lithium was investigated among dizygotic twins. The results indicate that lithium responders as a group show a more homogeneous pattern of lithium distribution across the red blood cell than do lithium nonresponders. In the second experiment the relationship between Li ratio and plasma lithium was investigated. The data indicate that the magnitude of this variation is insufficient to seriously affect the value of measuring the Li ratio. The third study reports on the different results obtained when measuring Li content by the indirect method and the direct method. The indirect method gives results that are more variable and therefore the direct method is recommended. 19 references.

003569 Misra, P. C.; Burns, B. H. Gartloch and Duke Street Hospital, Gartcosh, Glasgow 69, Scotland **"Lithium non-responders" in a lithium clinic.** Acta Psychiatrica Scandinavica (Kobenhaven). 55(1):32-40, 1977.

The outcome of long-term lithium maintenance therapy administered to 107 manic-depressive patients after more than 12 months was studied. Nine patients failed to respond despite having met the criteria for maintenance within the therapeutic range of lithium. This group, termed lithium nonresponders, had all shown bipolar illness with gross morbidity with frequent cycles, seven had a family history of affective illness (six bipolar). The study did not demonstrate any other clear factors common to the nonresponders group. 28 references. (Author abstract)

003570 Moizeszowicz, Julio; Subira, Segundo. 25 de Mayo 460, Buenos Aires, Argentina **Controlled trial of nomifensin (HOE 984) and viloxazine in the treatment of depression in the elderly.** Journal of Clinical Pharmacology. 17(1):81-83, 1977.

The antidepressant effects of nomifensin, a drug which is structurally unlike tricyclic antidepressants, were compared with those of viloxazine in a single blind trial in 40 elderly depressed patients. Antidepressant effects as assessed by the Hamilton Rating Scale (HRS) were produced by both drugs; however, from the second week of treatment on, nomifensin was superior to viloxazine in treating depression. No side-effects were reported spontaneously by the patients but sinus tachycardia was recorded in one viloxazine patient and in one nomifensin patient. 11 references.

003571 Pinta, Emil R. Dept. of Psychiatry, Ohio State University, 473 W. 12th Avenue, Columbus, OH 43210 **Deanol in Gilles de la Tourette Syndrome: a preliminary investigation.** Diseases of the Nervous System. 38(3):214-215, 1977.

A 31-year-old Negro male referred for treatment because of uncontrollable movements and periodic echolalia was treated with Deanol (dimethyl aminoethanol) to evaluate its effect in the Gilles de la Tourette Syndrome. The addition of Deanol to perphenazine did not result in an improvement of uncontrollable movements or involuntary speech utterances either as measured objectively or as reported by the patient. 11 references.

003572 Raleigh, Fred R., Jr. Atascadero State Hospital, Atascadero, CA 93422 **Reducing unnecessary antiparkison medication in antipsychotic therapy.** Journal of the American Pharmaceutical Association. NS17(2):101-102,106, 1977.

At Atascadero State Hospital two separate studies were conducted to determine the actual need for prophylactic administration of antiparkinson agents in conjunction with an-

tipsychotic medications. In both studies the dosage was eigher reduced or eliminated. The results demonstrated that there rarely is a need to administer antiparkinson medication prophylactically to patients on antipsychotic agents. If the antiparkinson agents are eventually required, most patients will require them for only short periods of time. Once used to the idea that prophylactic use of antiparkinson agents was unnecessary, the patients and the nursing staff realized many benefits. The most important benefit is elimination of unnecessary medication, thus reducing the chances of aggravation of psychosis. Also, elimination of unnecessary medication simplifies drug regimens and relieves nursing staff from time spent charting and administering superfluous medication. 11 references. (Author abstract modified)

003573 Schmidt, J. Psychiatric Hospital, DK-8240 Risskov, Denmark **Treatment of endogenous depressions with Thyrotropin-Releasing Hormone (TRH) under oral administration.** Acta Psychiatrica Scandinavica (Stockholm). 55(2):142-146, 1977.

In a double-blind study among six patients suffering from endogenous depression, three patients received thyrotropin releasing hormone (TRH) administered orally in doses of 20mg three times a day for 3 weeks. In an open controlled study of three patients suffering from endogenous depression, two patients received oral TRH 20mg four times a day for 2 weeks. Degree of depression according to Hamilton's Rating Scale measured during the study showed that TRH had no antidepressant effect. Thyroxine concentration in serum (T4) increased during the period of TRH treatment. 7 references. (Journal abstract)

003574 Siwers, B.; Borg, S.; d'Elia, G.; Lundin, G.; Forshell, G. Plym; Raotma, H.; Roman, G. Department of Psychiatry, Huddinge Hospital, S-141 86, Sweden **Comparative clinical evaluation of lofepramine and imipramine: pharmacological aspects.** Acta Psychiatrica Scandinavica (Kobenhaven). 55(1):21-31, 1977.

A multicenter comparative clinical evaluation of lofepramine, an imipramine analogue, and imipramine has been made with double-blind technique and fixed dosage. Plasma was drawn after 3 weeks for determination of noradrenaline uptake inhibitory capacity of the parent compound and/or its active metabolites. Plasma concentrations of lofepramine and desmethylimipramine (DMI) were determined in the same samples. The concentrations of lofepramine in the whole material were low except for one patient. In both groups of patients there was an almost 40-fold range in the plasma levels of DMI or apparent DMI. The patients were rated for severity of depression before treatment, then once weekly for 3 weeks and finally during the 5th week. A significant correlation was found between the concentrations of DMI and the noradrenaline correlations were found between the concentrations of DMI and the noradrenaline uptake inhibitory capacity in the plasma samples. No correlations were found between uptake inhibitory capacity of plasma samples and the amelioration scores. 26 references. (Author abstract)

003575 Stein, Johanna. Area D Community Mental Health Center, St. Elizabeths Hospital, Washington, DC 20032 **Tempo errors and mania.** American Journal of Psychiatry. 134(4):454-456, 1977.

The finding that a group of manic patients at a community mental health center responded optimally to tempo of musical selections played for them is noted, and the possibility that there is a relationship between tempo errors in a music task and mania is explored. The possibility of a manic diagnosis was raised in all 16 evaluation reports and was subsequently confirmed by psychiatrists' observations of 7 of the patients, who were then given therapeutic courses of lithium carbonate. Their condition stabilized rapidly, and within 1 to 2 weeks they slept normally, behaved and spoke realistically at a normal pace, and were not particularly irritable or suspicious. Soon thereafter, they became outpatients. 8 references.

003576 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Significance of biochemical parameters in the diagnosis, treatment, and prevention of depressive disorders.** Biological Psychiatry (Amsterdam). 12(1):101-131, 1977.

The evidence for a relationship between central 5-hydroxytryptamine (5HT) and the occurrence of certain types of depressions is reviewed. This evidence and the significance of biochemical parameters in the diagnosis is discussed. Cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) is derived from three sources: 1) postmortem studies; 2) measurement of treatment and prevention of depressive disorders; transport blackade by probenecid. Disturbances of central 5-HT metabolism are not typical for any depression but for certain types of vital (endogenous) depression. This implies that the group of vital depression, though tending towards homogeneity in terms of symptomatology, is heterogenous in biochemical terms and comprises patients with and without disorders in central 5-HT metabolism. It is plausible that disorders of the 5-HT metabolism play a role in the pathogeneis of depression, instead of resulting from them. This is based on the following findings: 1) 5-hydroxytryptophan (5-HTP) can abolish or alleviate the depressive syndrome or some of its elements; 2) this 5-HTP effect can be potentiated by clomipramine, a relatively selective inhibitor of 5-HT reuptake; and 3) there exists a negative correlation between 5-HT turnover in the CNS and the therapeutic effect of clomipramine. The alleged disturbances in central 5-HT are more likely to be predisposing than of direct causative significance. This assumption is based on two observations: 1) in more than 50% of cases, the 5-HT turnover remains low after clinical recovery, the patient being drug-free; and 2) there is suggestive evidence that abolition of the 5-HT deficit (by means of 5-HTP) exerts a prophylactic effect in uni and bipolar depression. 107 references. (Journal abstract modified)

003577 Yamhure, Alfonso; Villalobos, Alejandro. Division of Mental Health, Bogota, Columbia **Amoxapine: a double-blind comparative clinical study of amoxapine and amitriptyline in depressed hospitalized patients.** Current Therapeutic Research. 21(4):502-506, 1977.

In a 4 to 6 week study of 53 depressed patients, diagnosed as involutional melancholia or manic-depressive, and treated with amoxapine and amitriptyline, both drugs were generally equally effective, although omoxapine presented a faster therapeutic action. Statistically, both drugs showed similar potency, the most frequent doses being around 175mg per day for each one of them. Both groups of patients were comparable with respect to age, sex, weight, diagnostic classifications, and onset of illness. 5 references. (Author abstract)

003578 Young, Laurens D.; Keeler, Martin H. Department of Psychiatry and Mental Health Sciences, Medical College of Wisconsin, Milwaukee, WI 53226 **Sobering data on lithium in alcoholism.** Lancet (London). No. 8003:144, 1977.

Results of a 1 year study of therapeutic use of lithium carbonate in the treatment of alcoholic patients who also suffered

from bipolar affective disorder are presented. Results indicate that patients with concurrent diagnoses of alcoholism and bipolar affective disorder maintained on lithium show a greater morbidity from alcoholism than from affective illness. Therapeutic effectiveness of lithium was somewhat lower than had been expected on the basis of previous research. Data from this and other studies indicate that lithium may be effective against symptoms of alcoholism in only a subgroup of the alcohclic population with affective symptoms or that it may act directly to reduce alcoholic symptoms by a different mechanism from its antimanic or antidepressive activity. 5 references.

10 DRUG TRIALS IN NEUROSES

003579 Ananth, J.; Van den Steen, N. St. Mary's Hospital, 3830 Lacome Ave., Montreal, P.Q., H3T 1M5, Canada **Systematic studies in the treatment of obsessive compulsive neurosis with tricyclic antidepressants.** Current Therapeutic Research. 21(4):495-501, 1977.

In a systematic study, it was noted that even though both doxepin and chlorimipramine were effective in improving anxiety, statistically significant improvement of phobic symptoms was noted only with chlorimipramine. Chlorimipramine produced a significant increase in obsessive traits along with a significant decrease in the ability to resist obsessive symptoms while doxepin produced significant improvement in alleviating interference by obsessive symptoms. These findings indicate that chlorimipramine is a better therapeutic agent in obsessive-compulsive neurosis. Double-blind controlled studies to substantiate initial findings are in progress. 10 references. (Author abstract)

003580 Ban, T. A.; Lehmann, H. E.; Pecknold, J. C. Division of Psychopharmacology, Department of Psychiatry, McGill University, Montreal, Canada **Findings with a conditioning test battery: differential responsiveness to diazepam and doxepin.** Psychopharmacology Bulletin. 13(2):5-6, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, differential responses to diazepam and doxepin were studied in 40 patients with neuroses using a conditioning test battery. Before treatment, 14 of the 20 patients in the doxepin and 15 of the 20 patients in the diazepam group were tested and reclassified according to a specially devised conditioning procedure (SDCP). The reclassification was based on the SCP, which was carried out during one 30 to 60 min session in the course of which 61 to 181 stimuli (white and red lights) were administered and 8 conditioning variables were measured. The variables were: 1) presence of startle response on the Galvanic Skin Response; 2) acquisition of conditional reflex (CR); 3) extinction of CR; 4) disinhibition of extinguished CR; 5) reacquisition of CR; 6) generalization of CR; 7) differentiation of CR; and 8) reversal of CR. Pavlov's theory of experimental neurosis, referring to conflict induced excited or inhibited types of behavior, was the basis of patient reclassification. No statistically significant dif08/10/779in therapeutic efficacy between the two drugs was f group was judged improved by the Clinical Global Impressions Scale, Brief Psychiatric Rating Scale, and the Hamilton Anxiety Scale. There were indications that doxepin might be more clinically effective in inhibited patients, while diazepam might be more effective in excitable patients. 1 reference.

003581 Ban, Thomas A. Vanderbilt University, Nashville, TN 37203 **Perspectives in biological psychiatry: Part I. Mental deficiency, personality disorders, and neuroses.** Psychosomatics. 18(1):17-20, 1977.

Biological psychiatry is discussed in terms of mental deficiency, personality disorders, and neuroses. It is noted that simultaneously with the recognition that mental illness is not simply a violation of social norms, it has also become increasingly recognized that in the background of both functional and organic psychopathological syndromes, there are differential changes in various central nervous system structures. Among the clinical psychopathological conditions with early onset is mental deficiency that arises from inherent causes or is induced environmentally. One of the prototypes of genetically determined mental deficiencies is phenylketonuria; the favorable response to a low phenylalanine diet corresponds with the notion that the biochemical changes in phenylketonuria interfere with the development of normal behavior. No biochemical changes have been detected so far in personality disorders but psychometric and psychophysiological studies reveal that characteristics of some of these conditions is extroversion with low conditionability. It has been shown that by increasing the low conditionability of the psychopathic criminal with amphetamine, piperidyls, or trimethylxanthines, asocial criminals may be made accessible for educational training. The common occurrence of anxiety neuroses explains in part the extensive use of new anxiolytic sedative drugs. The drugs used in both anxiety and depressive neurosis and their mechanisms of actions are discussed.

003582 Barnes, Roy J. 5100 Poplar Avenue, Suite 3108, Memphis, TN 38137 **Mesoridazine (Serentil) in personality disorders -- a controlled trial in adolescent patients.** Diseases of the Nervous System. 38(4):258-264, 1977.

The efficacy and safety of mesoridazine (Serentil), in the form of 10mg tablets, in the treatment of symptoms associated with personality disorders was carried out in a double-blind study over a 6 week period in 30 adolescent patients. The average daily dose for the 15 patients in the mesoridazine group was 27.3mg in the first and 44.7mg in the sixth week. Mesoridazine relieved anxiety to a highly significant degree when compared with placebo and proved significantly more effective than placebo also in terms of mean improvement scores for depression and hostility. Significant reductions were likewise achieved in the overall severity of the disorders and in the severity of nearly all the other symptoms. The incidence of adverse reactions did not differ significantly from that following placebo administration. No extrapyramidal symptoms were noted. 9 references. (Author abstract modified)

003583 Brandrup, E.; Vanggaard, T. Psychiatric Department, Municipal Hospital, DK-4300 Holbaek, Denmark **LSD treatment in a severe case of compulsive neurosis.** Acta Psychiatrica Scandinavica (Stockholm). 55(2):127-141, 1977.

A detailed account is given of the course and outcome of the treatment with LSD of an incapacitating compulsive neurotic condition in a 30-year-old male. The treatment took place over 1 1/2 years from the autumn of 1962, and the patient, who has been followed since then, is completely cured symptomatically. In addition, a fortunate change in his general personality has taken place. The events during the LDS sessions revealed the basic elements of a development of his personality since early childhood, particularly the toilet training period, which resulted in a typical compulsive character neurosis. In turn, this character neurosis became the matrix for the outbreak of his manifest neurotic compulsions which began 4 years before the onset of treatment. The material which emerged was in complete accordance with Freudian theory.

No interpretations were given. While under the action of the drug the patient was left alone except for brief visits by the doctor or the nurse. He was free to call them if his anxiety became too strong for him to cope with alone. Besides, he had the support of reporting his experiences to the doctor after the LSD effect had worn off and discussing them during interviews between the LSD days, still without interpretations being given to him. Practical details of procedure are reported. The necessary caution in employing LSD for treatment purposes, especially the selection of patients, is emphasized; theoretical implications of the psychological material and the course of the curative process are discussed. 1 reference. (Journal abstract)

003584 Cox, J. R.; Pearson, Rosemary E.; Brand, Hilary L. Department of Geriatric Medicine, Nether Edge Hospital, Sheffield, England **Lithium in depression: a biochemical study.** Gerontology (Basel). 23(3):219-235, 1977.

Two groups of depressed patients, one with a history of recurrent depression and the other with a history of persistent apathy, were given lithium carbonate 1200mg g.i.d. and supplementary potassium 1200mg t.d.s. for 1 week. Measurements were made before and after the lithium treatment of total body water, extracellular fluid, total exchangeable sodium, and total exchangeable potassium, using sodium 24 and potassium 42 multiple isotope dilution techniques. After lithium treatment the values in the apathetic group showed little change, but the group with recurrent depression showed a significant increase in intracellular fluid and intracellular potassium, and a significant decrease in sodium. There was a marked mood increase in the group with recurrent depression but not in the apathetic group following lithium treatment. 30 references. (Author abstract modified)

003585 Devanthan, Saranya; Channabasavanna, S. M. National Institute of Mental Health and Neuro-Sciences, Bangalore 27, India **A controlled clinical study with clobazam -- a new anxiolytic agent.** Current Therapeutic Research. 21(3):361-367, 1977.

A controlled, double-blind clinical study of clobazam, a 1,5-benzodiazepine, in outpatients with anxiety neurosis is described. The subjects, 25 patients, were given 1 to 4 10mg capsules of clobazam/day, and their response compared to that of 22 patients receiving placebos. Each patient was assessed on the Hamilton Psychiatric Rating Scale for Anxiety (HARS) by 2 raters at the end of a 3 day placebo washout period and on days 8, 15, 22, and 29 of the test. On the same days, blood and urine tests were made. Clobazam reduced somatic and psychic anxiety levels at doses of 20 to 40mg/day. Improvement in the anxiety, fears, insomnia, cardiovascular and other autonomic symptoms, tension, depression, and general somatic sensory symptoms were found. The incidence of sedation was similar to that with other benzodiazepine derivatives. 9 references.

003586 Dorman, T. Pastures Hospital, Mickleover, Derby, England **Clinical trial comparison of two sustained release forms of amitriptyline.** Journal of International Medical Research (Northampton). 5(3):191-194, 1977.

A double-blind between group trial was carried out in 50 depressed patients to compare the efficacy of two sustained release forms of amitriptyline: Lentizol and Tryptizol 75. Patients received either Lentizol 50mg or Tryptizol 75 75mg each evening for the first week of the trial, and dosage was then doubled for a further 4 week trial period, with the proviso that dosage for individual patients could be maintained at, or altered to, original level where considered necessary by the investigator. Lentizol gave equivalent therapeutic effect to Tryptizol 75 despite the fact that overall dosage was one-third less than in the case of the latter. 10 references. (Author abstract)

003587 Dunn, C. Gibson; Gross, David. Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, MCV Station, Box 907, Richmond, VA 23298 **Treatment of depression in the medically ill geriatric patient: a case report.** American Journal of Psychiatry. 134(4):448-450, 1977.

A case study is presented of a 71-year-old man who was successfully treated for depression which had been diagnosed after his pulmonary clinical disability appeared out of proportion to his physical dysfunction. Treatment of choice was carefully administered tricyclic antidepressants. Arriving at a diagnosis of clinical depression in the medically ill geriatric patient can be difficult. The depression may present primarily with the signs of an organic brain syndrome (memory impairment, decreased cognitive abstractive ability), which may be assessed as an untreatable senile dementia. In addition, the elderly tend to deny dysphoric mood while acknowledging and emphasizing physical impairment. Furthermore, many neurovegetative and psychological symptoms suggestive of depression are pervasive in a medically ill population. The unfortunate outcome may be the patient's transfer to a chronic care facility until his/her death. 10 references.

003588 Free, Spencer M., Jr.; Overall, John E. Smith, Kline & French Laboratories, Philadelphia, PA **Validation of a physician rating scale for investigation of antianxiety effects of drugs.** Psychopharmacology Bulletin. 13(2):8-11, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the validity of the New Physician Rating List (NPRL) for investigation of antianxiety effects of drugs was studied and a new rating scale, Brief Outpatient Psychopathology Scale (BOPS) was described. The characteristics of the NPRL were evaluated using data from four double-blind studies designed to treat 328 patients with moderate to severe anxiety. Several factor analyses were carried out with the objective of identifying a factor structure that would include changes over time as well as individual differences among patients. Fifteen of 19 symptoms in the Total Morbidity Score (TMS) were assigned to one of four factors: anxiety, depression, psychomotor activation, and somatization. Statistically significant comparisons were identified among the study medications within each of the four factors and the TMS. Based on the results, the BOPS was devised containing 15 symptoms. The proposed factor structure included: 1) anxiety (anxiety, tension, uneasiness); 2) depression (depressive mood, feeling of inferiority, loss of interest); 3) psychomotor activation (hyperactivity, agitation, motor disturbance); and 4) somatization (psychophysiological disturbances, hypochrondriasis, skeletal muscular disturbances). In addition, guilt feelings, fatigue, and sleep disturbances were included in the TMS.

003589 Goldberg, H. L.; Finnerty, R. J. West-Ros-Park, Mental Health Center, 26 Central Avenue, Hyde Park, MA 02136 **A double-blind study of Prazepam versus placebo in single daily doses in the treatment of anxiety.** Comprehensive Psychiatry. 18(2):147-155, 1977.

Thirty anxious outpatients were given Prazepam and 29 were given placebo in a test of the efficacy of a once a day bedtime dose of Prazepam for the treatment of anxiety. On

both the patients' and psychiatrists' ratings of global improvement, Prazepam, taken once a day at bedtime in doses of 20mg to 40mg, was significantly better than placebo in these private patients with anxiety symptoms. The patient ratings of global improvement, on which Prazepam was shown to be better than placebo, were: 1) the patient's opinion of how much he or she had changed at each visit since the study onset; and 2) the patient's evaluation at the end of treatment of how much the study drug helped. The psychiatrist ratings of global improvement, on which Prazepam was shown to be better than placebo, were: 1) the psychiatrist's evaluation of the degree of global psychopathology at each patient vist; 2) the psychiatrist's opinion of the change in the patient at each visit since the study onset; and 3) the psychiatrist's evaluation at the end of treatment of the therapeutic effect of the study drug. 9 references.

003590 Goldberg, Solomon C.; Halmi, Katherine A.; Eckert, Elke; Casper, Regina; Davis, John. NIMH, 5600 Fishers Lane, Rockville, MD 20857 **Cyproheptadine in anorexia nervosa. (Unpublished paper).** Rockville, MD, NIMH, 1977. 9 p.

An investigation into the efficacy of cyproheptadine HCL (Periactin) in inducing weight gain in severely emaciated anorexia nervosa patients was reported to the Annual Meeting of the American Psychiatric Association held May 1977 in Ontario Canada. Eighty one female patients satisfying rigorous diagnostic criteria for anorexia nervosa in three participating hospitals were randomly allocated to one of four treatment combinations: 1) Periactin and behavior modification; 2) Periactin and no behavior modification; 3) placebo and behavior modification; 4) placebo and no behavior modification. Patients were treated in hospital for 35 days. Periactin was found to be effective in a subgroup of anorexia nervosa patients who: 1) had a history of birth delivery complications: 2) were more emaciated (41-52% weight loss from norm) on entering the study; and 3) had a history of prior outpatient treatment failures (less than 2 kg weight gain). The results imply that this subgroup is diagnostically separate from those who do not respond to Periactin. A companion paper on behavior modification shows that treatment to be effective on a subgroup who have no history of prior outpatient treatment of adequate (12 weeks) duration. Thus, the data suggest that Periactin and behavior modification are both effective but on opposite subgroups; Periactin on the more severe form and behavior modification on the less severe form. 12 references. (Author abstract)

003591 Kellner, Robert; Bruzzese, Domenic; Winslow, Walter W. Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM 87106 **Brief treatment of anxious patients with halazepam in high doses.** Psychopharmacology Bulletin. 13(2):21-22, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation 9 units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, 20 nonpsychotic inpatients suffering from moderate to severe anxiety were treated with high doses of halazepam in a 2 day crossover trial. Nine patients were given small doses of amobarbital on the prestudy day because they were severely distressed. Chloral hydrate was given as night sedation thoroughout the study to 19 patients. The starting dose was 40mg; each patient was interviewed at 2 hour intervals and if he was still anxious and had no substantial side-effects, the dose was increased. The doses of halazepam ranged from 100 to 600mg daily, median 600mg. All observer ratingss and self-ratings favored halazepam over placebo. There was a tendency for patients to report more drowsiness on drug days. The results suggest that the design of this study can be used for the rapid screening of antianxiety properties of drugs and also suggest that overt symptoms of anxiety can be controlled in a very short time in a large proportion of severely distressed patients by individually adjusting the dose at frequent intervals. 2 references.

003592 Kellner, Robert; Sheffield, Brian F.; Simpson, George M. Department of Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM 87106 **Comparative value of rating and self-rating scales in drug trials.** Psychopharmacology Bulletin. 13(2):12-14, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the comparative value of rating and self-rating scales in drug trials is discussed and the results of one study which compared the sensitivity of several self-rating scales are presented. The self-rating scales used were: 1) the short form of the Symptom Rating Test (SR) in which 30 symptoms are rated on a four point box scale from "not at all" to "extremely"; 2) the Symptom Questionnaire (SQ) in which 60 symptoms and statements of well-being are checked as true or false; and 3) the Brief Distress Scale (BDS) in which 14 symptoms are rated on nine point graphic scales. Global observer rating scales and the Hamilton Anxiety Rating Scale (HARS) were also used. In a double-blind crossover trial of chlordiazepoxide and placebo of 22 patients, all total scores and all 11 subscores of the self-rating scales discriminated significantly between drug and placebo; the HARS did not. When the sample size was reduced in order to examine which of the self-rating scales was the most sensitive, two of the scales still discriminated significantly between the treatments. In another subsample, the BDS was somewhat less sensitive than the SQ and SRT. The results suggest that it is possible to construct self-rating scales which even with the average clinic population are either as sensitive as or perhaps more sensitive than commonly used observer rating scales. 6 references.

003593 Klein, Donald F.; Zitrin, Charlotte M.; Woerner, Margaret G. Long Island Jewish-Hillside Medical Center, Hillside Division, Glen Oaks, NY 11004 **Imipramine and phobia.** Psychopharmacology Bulletin. 13(2):24-27, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the efficacy of behavior therapy with imipramine (BTI), behavior therapy with placebo (BTP), and supportive therapy with imipramine (STI) were studied in 172 patients with phobias. The BTI and BTP studies were double-blind and the STI study was single-blind. The patients were divided into three groups: 1) agoraphobics, who have spontaneous panic attacks and anticipatory anxiety; 2) phobic neurosis patients, who have severe anxiety only in connection with specific situations; and 3) mixed phobics, who combined some qualities of the other groups but were not typical of either. There was a nonsignificant trend indicating a higher dropout rate for patients on imipramine (I) than on placebo; the total dropout rate was 23%. The results on 111 patients that completed treatment confirm the hypothesis that imipramine alleviates the spontaneous attacks of agoraphobics and mixed phobics, but therapist ratings did not significantly differentiate the BTI and BTP conditions for agoraphobics. As expected for the phobic neurosis patients there was no difference between the imipramine and placebo conditions. Behavior therapy was not superior over supportive therapy for any group. Of 59 patients followed up for 1 year, 12 relapsed; there were no significant differences in relapse rate between diagnostic groups and treatment conditions. 4 references.

003594 Lavallee, Yvon-Jacques; Lamontagne, Yves; Pinard, Gilbert; Annable, Lawrence; Tetreault, Leon. Institut National de la Recherche Scientifique, Montreal H1N 3M5, Canada **Effects on EMG feedback, diazepam and their combination on chronic anxiety.** Journal of Psychosomatic Research (Oxford). 21(1):65-71, 1977.

The effects of electromyogram (EMG) feedback (the most clinically promising of the biofeedback techniques) and diazepam, alone and in combination, on patients suffering from chronic free floating anxiety were assessed. Forty patients were randomly assigned to one of four groups in a 2 x 2 factorial design: EMG feedback plus diazepam, EMG feedback plus diazepam placebo, EMG control (no feedback) plus diazepam and EMG control (no feedback) plus diazepam placebo. During treatment, the effects of EMG feedback plus diazepam were additive in reducing muscular tension. Although all active treatment groups reduced their anxiety after treatment, diazepam treated subjects (with or without feedback) did less well than other subjects on anxiety measurements, adjuvant medication usage and home practice. The results indicate that EMG feedback treatment without diazepam had a more prolonged therapeutic effect for chronic anxious patients. 17 references. (Author abstract modified)

003595 Ostfeld, Adrian; Smith, Cedric M.; Stotsky, Bernard A. Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College St., New Haven, CT 06510 **The systemic use of procaine in the treatment of the elderly: a review.** Journal of the American Geriatrics Society. 25(1):1-19, 1977.

The world literature on the systemic use of procaine in the treatment of the aging process and the common chronic diseases of later life is reviewed and evaluated. Included are data from 285 articles and books, describing treatment in more than 100,000 patients in the past 25 years. Except for a possible antidepressant effect, there is no convincing evidence that procaine (or Gerovital, of which procaine is the major component) has any value in the treatment of disease in older patients. If procaine has an antidepressant effect, there is some likelihood that this accounts for the reports of decreased complaints referable to the musculoskeletal, cardiovascular, endocrine, sexual, gastrointestinal and respiratory systems. 148 references. (Journal abstract modified)

003596 Overall, John E. University of Texas Medical Branch, Galveston, TX **Is the drug effect antianxiety or antidepressant?** Psychopharmacology Bulletin. 13(2):11-12, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the question of whether the effects of drugs used to treat patients with mixed anxiety and depression is antianxiety, antidepressant, or both was investigated using data from four double-blind studies of low dose phenothiazine versus placebo in the treatment of anxious depressed outpatients. Analyses of simple change scores for anxiety and depression factors separately revealed a highly significant difference between drug and placebo in producing improvement on each factor separately. Both the change in anxiety with change in depression partialed out and the change in depression with change in anxiety partialed out revealed no difference between drug and placebo. The results lend further support to the concept of anxious depression as a primary syndrome in which neither anxiety nor depression can be segregated as the target of drug treatment and suggest that chemotherapeutic intervention affects an underlying process that is responsible for both types of symptoms.

003597 Rickels, K.; Sablosky, L.; Silverman, H.; Case, W. G.; Rial, W.; Mirman, M.; Gottlieb, S. 203 Piersol Building, 3600 Spruce Street, Hospital of the University of Pennsylvania, Philadelphia, PA 19104 **Prazepam in anxiety: a controlled clinical trial.** Comprehensive Psychiatry. 18(3):239-249, 1977.

A report of a 4 week double-blind study undertaken to determine the optimum daily dosage of prazepam is presented. The drug and a placebo were administered at bedtime to two groups of patients with moderate anxiety in daily dosages of 40 and 60mg. Results of the study indicated that prazepam is an effective agent for the relief of anxiety. After 2 weeks treatment, marked improvement was noted in patients who received 60mg of nighttime dosage. However, by 4 weeks, patients on prazepam 40mg dosage had caught up with and occasionally surpassed the improvement shown by the 60mg patients. In both prazepam groups, the patients improved significantly more than those in the placebo group. Sedative side-effects were most often experienced by patients on 60mg of prazepam. 6 references.

003598 Rickels, Karl. Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104 **Non-specific factors in drug treatment.** In: Brady, J., Psychiatry: areas of promise and advancement. New York, Spectrum, 1977. 253 p. (p. 159-170).

Based on research performed at the University of Pennsylvania, major nonspecific variables affecting psychopharmacological treatment outcomes of anxious neurotics are discussed. Physician attributes found to be relevant to good treatment response with anxiolytic agents are empathy, emotional warmth, positive attitude toward the psychopharmacotherapy, and a good prognosis for the patient. Patient personality characteristics which correlate with good response include verbal intelligence, compliance, realistic treatment goals, high ego strength, and low verbal hostility. Neurotic psychopathology predictors of improvement are: more severe somatization, less severe obsession compulsion, less severe interpersonal sensitivity, more severe anxiety, and less severe depression. Social advantage, treatment orientation, and prior treatment characteristics also influence positive outcome. It is concluded that a knowledge of these factors can be used to improve patient response and enhance the psychotherapeutic situation. 21 references.

003599 Rickels, Karl; Downing, Robert W. University of Pennsylvania, Philadelphia, PA 19104 **Prazepam in anxiety: a controlled clinical trial.** Psychopharmacology Bulletin. 13(2):19-21, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, in a double-blind controlled clinical trial of prazepam, 103 patients with at least moderate anxiety were treated once a day at bedtime with either 40mg prazepam (P40), 60mg prazepam (P60), or placebo. Attrition rate was 33%. A greater number of the early dropouts came from the P60 group than the other two groups. Fifteen patients were taken off medication because of side-effects (7 on P60, 4 on P40, and 4 on placebo). Side-effects occurred mostly within the last 4 days of treatment and were of a sedative nature; P60 produced the largest number of side-effects. At 2 weeks, P40 and P60 produced significantly more improvement than placebo in two physician completed anxiety questionnaires and in several global improvement ratings. P60 was generally more effective than P40. After 4 weeks, P40 had become as effective as P60, but only by combining the two prazepam groups could prazepam be shown to be more effective than placebo.

Improvement in insomnia for prazepam patients was equally high for those who did and did not experience global improvement, suggesting that the effectiveness of prazepam was not merely a function of its hypnotic properties.

003600 Rickels, Karl; Pereira-Ogan, Jorge; Csanalosi, Irma; Morris, Richard J.; Rosenfeld, Howard; Sablosky, Lester; Schless, Arthur; Werblowsky, Joshua H. University of Pennsylvania, Psychopharmacology Research Unit, 203 Piersol Bldg., University Hospital, Philadelphia, PA 19104 **Halazepam and diazepam in neurotic anxiety: a double-blind study.** Psychopharmacology (Berlin). 52(2):129-136, 1977.

Halazepam (HZ) was compared to diazepam (DZ) and to a placebo in a double-blind study with anxious neurotic outpatients from general family practice (GP) and symptomatic volunteer clinic (SVC). At least 4 weeks treatment was completed by 125 patients. HZ produced more side-effects than DZ, the most common being sedation. DZ was slightly more effective than HZ according to several outcome criteria. At the 6 wk period, DZ was significantly more effective according to physician and patient questionnaire ratings. Global ratings, however, indicated the drugs to be equally effective. Anxious patients with little secondary depression improved more than patients with more marked secondary depression regardless of treatment. High anxious HZ treated patients improved significantly more than low anxious HZ treated patients, while initial level of anxiety showed little effect on the DZ response. No significant drug x population interaction effects were found and only very few population effects occurred indicating SVC patients to improve more than GP patients. 6 references. (Author abstract modified)

003601 Ross, W. Donald. University of Cincinnati College of Medicine, Cincinnati, OH **Treating depressed cardiac patients.** Ohio State Medical Journal. 73(1):21-24, 1977.

Depression treatment in patients with heart disease is discussed, noting that depression frequently follows cardiac infarction and may lead to delayed convalescence and persistent or recurring congestive heart failure. Psychotherapeutic measures which may be used by the physician are described. It is suggested that the physician should recognize the possibility of depression or other emotional stress as a cause of heart failure. The pharmacologic problems concerning effects of psychotropic drugs on the heart are reviewed. Most antidepressants and electroconvulsive therapy are contraindicated for heart disease patients; however, it has been found that the tricyclic antidepressant, doxepine hydrochloride, can be used safely if started in small doses and monitored closely. Doxepin is described as the drug of choice for severe depression in elderly people, with or without electrocardiographic changes. 23 references. (Author abstract modified)

003602 Shammas, Elia. One Randall Square, Providence, RI 02904 **Controlled comparison of bromazepam, amitriptyline, and placebo in anxiety-depressive neurosis.** Diseases of the Nervous System. 38(3):201-207, 1977.

Private practice patients (N=72) with moderate or severe anxiety depressive neurosis received mean daily oral doses of 23.8mg bromazepam, 94mg amitriptyline, or 4.6capsules of placebo in a double-blind study over 4 weeks to compare the relative clinical response to these drugs. A larger degree of improvement in a greater number of patients occurred with bromazepam. Amitriptyline produced significantly more severe reactions than bromazepam. It is suggested that the rapid clinical response to bromazepam contributed toward its superior safety and patient progress because it was possible to titrate dosage, thereby helping to control adverse reactions and allowing patients to remain alert and productive during therapy. 16 references. (Author abstract modified)

003603 Shurley, Jay T.; Lawrence, Betsy E.; Spalding, James C.; Fishkin, Steven M.; Pishkin, Vladimir. VA Hospital, Oklahoma City, OK 73104 **A clinical comparative evaluation of doxepin and chlordiazepoxide in psychoneurotic inpatients.** Current Therapeutic Research. 21(4):518-523, 1977.

A controlled, double-blind study of 48 depressed and/or anxious psychiatric inpatients showed that doxepin was as effective as chlordiazepoxide in reducing symptoms of anxiety over a 2 week period, and was more effective in reducing psychological measures and in improving global clinical ratings of depression. Clinical side-effects were few for either drug, and those found with doxepin were milder than those noted for chlordiazepoxide. Results must be cautiously interpreted, since hospitalized controls also showed significant changes. No changes were found for hostility or trait anxiety as measured by the Zuckerman and the Taylor manifest anxiety scale, respectively. 10 references. (Author abstract)

003604 Silverstone, J. T.; Carne, H. J.; Dell, A.; Franklin, C. J. G.; Singer, R.; Swirsky, S. N.; Forrest, W. A. St. Bartholomew's Hospital, London, England **A comparison of maprotiline and amitriptyline in the treatment of depression in general practice.** Practitioner (London). 218(1304):279-282, 1977.

Forty patients (27 women and 13 men) with a mean age of 45 years were treated for depression with maprotiline (M) or amitriptyline (A) in a between patient double-blind trial administered by five general practitioners working as a group in collaboration with a consulting psychiatrist. Patients were rated by their own physician at day 0, 7, 14, and 21 by the Hamilton rating scale (HRS) for depression and on day 21, both patient and physician made their own evaluations using a 5 point global rating scale. Three patients in the A group dropped out because of severe side-effects, and two patients in each group dropped out for unknown reasons. By day 21, both M and A had produced a considerable and significant reduction in the mean HRS scores and there was no significant difference between them. However on day 7, the improvement in the HRS score of the M group was almost twice that of the A group. On global ratings, only six patients were judged not to have improved, one of which, treated with A, rated worse than on day 0. The results suggest that M might be a useful drug for treatment of depression in general practice. 5 references.

003605 Vanov, S. K.; Arrington, W. S.; Richards, D. J. Wyeth Laboratories, Philadelphia, PA **A multiclinic double-blind trial of the anxiolytic properties of lorazepam in psychiatric outpatient practice.** Psychopharmacology Bulletin. 13(2):17-19, 1977.

In a paper presented to a meeting of the Early clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the anxiolytic properties of lorazepam were studied by 12 independent psychiatrists in a double-blind trial using a parallel design with a duration of 4 weeks. The outpatients in the study had at least moderate anxiety as judged by the physician rated global scale and a moderate to severe score on anxious mood and three other items on the physician rated Hamilton Anxiety Scale. The results indicated that lorazepam provided a significantly greater relief of anxiety, both statistically and clinically, than the placebo. Side-effects were by and large mild and transient and were either con-

trolled by dose change or disappeared with continued treatment. Treatment was discontinued in only 26 (7%) of the patients on lorazepam and 17 (5%) on placebo. It was concluded that a multiclinic trial has several advantages including: 1) a large sample size which permits an active therapy to be identified even in the presence of a high placebo response; and 2) the evaluation of a new drug in a broad sample of patients seen by many different psychiatrists, which provides a more accurate reflection of safety and efficacy than the results of a single study. 1 reference.

003606 Versiani, Marcio; Bueno, J.; Mundim, F. Institute of Psychiatry, Federal University of Rio de Janeiro, Brazil **A double-blind comparison between loxapine and chlordiazepoxide in the treatment of anxiety.** Psychopharmacology Bulletin. 13(2):22-24, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, 52 patients with a diagnosis of neurosis with predominant symptoms of anxiety were studied in a double-blind comparison between loxapine (L) and chlordiazepoxide (C). Treatment was initiated after a washout period of 1 week; after the 1st week dosage was adjusted according to individual responses. Mean dosages in the 4th week were 50mg chlordiazepoxide and 9mg loxapin; at the end of the 4th week, medication was abruptly discontinued and withdrawal symptoms and/or deterioration of psychiatric condition were assessed. There was significant improvement in most items and factors of the Hamilton Rating Scale for Anxiety, Self-Rating Symptom Scale, and Clinical Global Impressions at the end of the 1st week; deterioration was detected during the 5th week. The most common side-effect in both groups was sleepiness. The results indicate that with respect to efficacy and/or tolerance the two drugs were comparable when used at a 1:5 ratio. The lack of a placebo group in the trial diminished the possibility of assessing the accuracy of the experiment. 6 references.

003607 Wang, Richard I. H.; Larson, Craig. Veterans Administration Center, Wood, WI 53193 **New anxiolytic rating scale.** Psychopharmacology Bulletin. 13(2):6-8, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, a new anxiolytic rating scale, the Wang Anxiety Rating Scale (WARS) was tested by using it in conjunction with the Hamilton Anxiety Rating Scale (HARS), the Global Illness scale and an Anxiety Adjunct Scale (AAS) to evaluate subjects during two separate clinical investigations of clorazepate and lorazepam. The WARS contains the following items: nervousness, restlessness, excitability, irritability, worrying, disturbed concentration, hostility, palpitation, insomnia, tremors, smoking, and excessive perspiration. Some somatic complaints often included in anxiety rating scales were excluded from the WARS and were put, with other commonly reported drug effects, in the AAS. The HARS and WARS had a highly significant correlation with the exception of the premedication value in the clorazepate study, which approached significance. The AAS showed greater correlation with the HARS than with the WARS. In the clorazepate study, both the HARS and the WARS correlated significantly with the Global Illness scale; however, the WARS correlated to a higher degree in all periods. It was concluded that the WARS meets the requirements of a useful rating scale for evaluating treatment effects of anxiolytics, is not influenced by emergent side-effects, as the HARS appears to be, and is easy to administer. 2 references.

003608 Waxman, D. Department of Psychological Medicine, Central Middlesex Hospital, London, England **The management of phobic disorders using clomipramine (Anafranil).** Journal of International Medical Research (Northampton). 5(Supplement 1):24-31, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the management of phobic disorders using clomipramine was discussed. The problem of phobic anxiety is viewed in the context of the entire area of mental illness and of its epidemiology in the general population. The importance of the diagnosis of depression in phobic patients and its simultaneous treatment is emphasized. Psychotherapeutic and psychopharmacological methods are discussed and some results of recent trials of clomipramine are reported. It is concluded that for the successful outcome of treatment an eclectic approach must be considered. The combination of behavioral techniques of desensitization along a hierarchy of anxiety provoking situations, together with psychotherapeutic support and the simultaneous exhibition of the more specific antidepressant and antiphobic preparation clomipramine would offer the best hope of symptom relief. 32 references. (Journal abstract modified)

003609 Wheatley, David. General Practitioner Research Group, Twickenham, England **Antianxiety drug trials in hypertension.** Psychopharmacology Bulletin. 13(2):27-30, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, to test the hypothesis that antianxiety drugs might play a part in the control of hypertension by drug therapy, 71 patients were treated in a double-blind study with methyldopa plus placebo or medazepam, and 78 patients were treated with either propranolol or methyldopa. Although the relief of anxiety symptoms was associated with reduction of blood pressure, the effect was nonspecific and was not influenced by either medazepam or propranolol. The possibility that methyldopa might, per se, exert some antianxiety effects was pointed out. The results indicate that the general use of antianxiety drugs in hypertension would appear to be contraindicated, although their use in individual cases might contribute to the well-being of the patient while not exerting a direct influence on the response to treatment. 3 references.

11 DRUG TRIALS IN MISCELLANEOUS DIAGNOSTIC GROUPS

003610 Barcai, A. 2 Ra-Ashi St., Tel-Aviv, Israel **Lithium in adult anorexia nervosa: a pilot report on two patients.** Acta Psychiatrica Scandinavica (Stockholm). 55(2):97-101, 1977.

Two patients suffering from anorexia nervosa for many years who wished to gain weight were treated successfully with lithium carbonate. One patient gained 12 kg and the other 9 kg within 6 weeks. The weight gain was maintained for a year of followup with lithium maintenance therapy. It is suggested that such treatment be confined to adults, particularly in view of the tendency for fluid trapping and electrolyte balance changes which frequently accompany lithium treatment. 19 references. (Journal abstract modified)

003611 Bassot, Jacques. no address **/Parkinson's disease: a therapeutic memorandum./** La maladie de Parkinson: aide-memoire therapeutique. Revue de Geriatrie (Paris). 2(1):159-161, 1977.

Therapy of Parkinson's disease in the aged is reviewed. The present therapies for the Parkinson's disease aim at replacing in situ the dopamine which is lacking, totally or partly. L-dopa

is the major remedy, but it has also undesirable secondary effects. Fortunately, with equal effectiveness, the inhibitors make it possible to reduce the active dose and therefore to decrease these secondary effects. Other therapies are still valuable, alone or associated: anticholinergic, amantadine, readaptation, psychotropic drugs and psychotherapy. These therapies are briefly discussed. (Journal abstract)

003612 Brodie, N. H. no address **A double-blind trial of naftidrofuryl in treating confused elderly patients in general practice.** Practitioner (London). 218(1304):274-278, 1977.

Sixty confused elderly patients (66-89-years-old) were treated with naftidrofuryl (N) or placebo in a double-blind trial by 8 general practitioners for 2 months. The patients had at least one of the following: 1) disturbance in intellectual functioning; 2) difficulty in coping with routine daily activities; and 3) disturbances in relationships with others and with evidence of progressive withdrawal and reduced motivation. Both groups of patients showed significant improvement over their intial scores on an intelligence scale. Overall activity improved in significantly more patients after N than after placebo. Although there was similar improvement in recreation activity in both groups, there was a highly significant difference in favor of N if the other activity groups: 1) chores around the house; 2) personal care; and 3) outdoor activity were considered separately. The physicians overall assessment showed a significant advantage for the N group. Seven of the 29 patients on N and 1 patient on placebo exhibited side-effects, but none were serious enough to warrant change in therapy. The results suggest that in future studies of the assessment of primary senile dementia in general practice, less importance should be attached to improvement on an intellectual scale, since observation of daily living activities is a more accurate reflection of the overall condition. 11 references.

003613 Chiland, Colette. University of Paris, Paris, France **Long-term treatments of psychotic states.** New York, Human Sciences Press, 1977. 254 p. $37.95.

Contributions to the subject of long-term treatment of psychotic states in terms of epidemiology, etiology, chronicity, and treatment are presented. Topics covered include general problems relating to psychosis, including long-term drug therapy; therapeutic experiences and experiments with psychotic children and chronic schizophrenics; experiences at Chestnut Lodge, Austen Riggs Center, and the Massachusetts Mental Health Center; transcultural studies; and reflections on the psychiatrist in the community, including a discussion of community based treatment.

003614 Dilts, Stephen L.; Keleher, Denis L.; Hoge, George; Haglund, Bonita. Alcoholism Treatment and Rehabilitation Program, Denver General Hospital, West 8th Ave. and Cherokee St., Denver, CO 80204 **Hydroxyzine in the treatment of alcohol withdrawal.** American Journal of Psychiatry. 134(1):92-93, 1977.

The efficacy of hydroxzine in the treatment of alcohol withdrawal was assessed in 121 inpatient alcoholics, and its effect were compared with those of clorazepate dipotassium. Results revealed no complications in the clorazepate group and complications in 6 patients in the hydroxyzine group. These complications included delirium tremens, agitation, and autonomic dysfunction. Antipsychotic drugs were used to combat these symptoms and had to be administered in higher doses than when used with benzodiazepines. It is concluded that hydroxyzine is less effective than clorazepate in reducing the complications of the alcohol withdrawal syndrome and that it does not offer the full range of symptom control provided by the benzodiazepines. 3 references.

003615 Ehrensing, Rudolph H.; Kastin, Abba J.; Larsons, Paul F.; Bishop, George A. Dept. of Psychiatry, Ochsner Clinic, 1514 Jefferson Hwy., New Orleans, LA 70121 **Melanocyte-stimulating-hormone release-inhibiting factor-I and tardive dyskinesia.** Diseases of the Nervous System. 38(4):303-307, 1977.

The use of melanocyte stimulating hormone release inhibiting factor I (MIF-I) in treatment of 13 chronically institutionalized patients with moderate to severe tardive dyskinesia was studied. Patients received MIF-I orally for 7 weeks in doses up to 2500mg daily. A rating scale for tardive dyskinesia (shown in an addendum), as well as other psychiatric tests and physiological analyses were used to evaluate patient progress. A significant but transient decrease in severity and frequency of symptoms was seen in the nine women patients with only lower doses of MIF-I. This improvement was judged to be a placebo effect. A less likely explanation postulated was that MIF-I has a biphasic, dose related response. 18 references.

003616 Elliott, Frank A. Dept. of Neurology, Pennsylvania Hospital, Philadelphia, PA 19107 **Propranolol for the control of belligerent behavior following acute brain damage.** Annals of Neurology. 1(5):489-491, 1977.

The use of propranolol for control of belligerent behavior following acute brain damage was investigated. The belligerence of seven patients who had suffered an acute brain insult was effectively controlled by propranolol in doses of 60 to 320mg per day. Of the seven patients, three were treated in the acute stage after a stroke, a severe closed head injury, and a gunshot wound of the brain, respectively. A chronic postconcussion syndrome associated with chronic irritability was present in two and two were not chronically irritable but suffered from intermittent attacks of explosive rage in response to minor irritations. In all instances the belligerent behavior was controlled without inducing general sedation. 10 references. (Author abstract modified)

003617 Fabre, Louis F., Jr.; Gainey, Allison; Kemple, Sherrie. Research Testing Inc., The Fabre Clinic, 5503 Crawford Street, Houston, TX **Pilot open-label study of alprazolam(U-31,889) in anxious alcoholic outpatients.** Journal of International Medical Research (Northampton). 5(1):26-32, 1977.

In order to determine the anxiolytic efficacy and the safety of alprazolam(U-31889) a triazolobenzodiazepine, 20 outpatients suffering from anxiety and tension after withdrawal from alcohol were treated for 28 days with alprazolam. Three patients dropped out for intercurrent events, and two dropped out for recurrent drinking. Of the 15 patients completing the study, analysis of variance showed significant improvement in all Physician's Ratings as well as all patient self-ratings. At the 28th day, 93% of the patients rated moderated to marked improvement on the Physician's Global Impression and Therapeutic Effect, and 93% self-rated at least a little better. Side-effects were generally mild and inconsequential. No adverse effects attributable to to alprazolam were noted on laboratory evaluations, EKGs, or ophthalmologic examinations. 11 references. (Author abstract)

003618 Fromm, Gerhard H.; Wessel, Henry B. no address **Imipramine in absence and minor motor seizures: double-blind study and long-term follow-up.** Neurology. 27(4):370, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, imipramine was tested in a double-blind, crossover study of 10 patients with absence and minor motor seizures who had not responded to conventional medications and in an open trial of 17 patients; followup was long-term in both groups. In the first group imipramine produced an initial decrease in seizure frequency in 6/10 and the beneficial effect was maintained in 2 for more than 1 year. Imipramine produced an initial reduction in seizure frequency in about 60 percent and long-term benefit in 20 percent of the 17 patients. The validity of the experimental model was confirmed by the fact that imipramine decreased the frequency of absence and minor motor seizures in more than half the patients. The results suggest that it is another drug to use in the treatment of a disorder that is notoriously refractory to all therapeutic regimens currently available.

003619 Gilbert, Michael M. 316 N.E. 14 Terrace, Miami, FL **The efficacy of percogesic in relief of musculoskeletal pain associated with anxiety.** Psychosomatics. 17(4):190-193, 1977.

A double-blind study to determine if the combination of a tranquilizer and an analgesic produces more effective pain relief than either agent alone was presented. The rationale behind the study is that in the symptomatic treatment of pain, not only the physical transmission of the painful stimulus but also the various emotional and psychological factors effecting its total perception must attacked. The Ss were 160 adult patients with acute episodes of mild to moderate traumatic of nonrheumatic musculoskeletal pain associated with anxiety. The patients were assigned to one of four medication groups: acetaminophen alone, pheyltoloxamine (Percogesic) alone, acetaminophen plua phenytoloxaimen, or a placebo. Phenytoloxamine is a benzylphenol known to have tranquilizing and ataractic effects without excessive sedation. Acetaminophen is an established analgesic without the tendency toward gastric irritation ascribed to aspirin. All the patients were evaluated for drug effect one hour after the first dose and again after one and two days of therapy. At each evaluation the following measurements were employed: 1) A five item symptom evaluation by the physician; 2) the Hamilton Anxiety Scale; and 3) physician's global evaluation of drug effect on pain and anxiety. The results indicated that the combination of acetaminophen and phenyltoloxamine was more effective in relieving pain accompanied by anxiety than either drug when used alone. 5 references.

003620 Gittelman, Rachel. Queens College, City University of New York, Flushing, NY 11367 **Preliminary report on the efficacy of methylphenidate and behavior modification in hyperkinetic children.** Psychopharmacology Bulletin. 13(2):53-54, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, preliminary data were presented on an 8 week study of the treatment of 34 hyperkinetic children (6-12-years-old) with methylphenidate (MP), behavior therapy following operant conditioning principles and placebo (BT), or BT and methylphenidate (BTMP). All three treatments produced improvement as rated by teachers on the conduct disorder, inattention, and hyperactivity factors; however, the MP and BTMP groups rated better than the BT group. The teachers' posttreatment scale ratings of the children on medication were identical to ratings of normal children, whereas the BT group was more pathological than normal children. Teachers' evaluation on global improvement showed the BTMP group to be improved more than the BT group. Psychiatrists' global ratings agreed with the teachers', but the mothers' global improvement ratings revealed no treatment differences. A trend was found in favor of MP and BTMP in classroom observations, with MP or BTMP being significantly superior to BT in reducing minor motor movements. The results suggest that if medication is not enough for hyperkinetic children, then behavior modification should be added, rather than the reverse. 2 references.

003621 Gostick, N. K. no address **A comparison of various clomipramine (Anafranil) dosage regimes.** Journal of International Medical Research (Northampton). 5(Supplement 1): 2-10, 1977.

At a symposium held at Rabat, Malta, in November, 1976, a multicenter general practitioner trial was discussed comparing four dosage regimes of clomipramine: 10mg t.d.s.;30mg o.n.;25mg t.d.s.;and 75mg o.n. The clinical results were obtained using a series of twelve visual analogue scales completed independently by doctor and patient. Also side-effects, recorded on a standard list of unwanted effects of tricyclic antidepressants, were studied. Very few statistical differences were found between the dosage regimes, and they were difficult to interpret clinically. It was concluded that although 25mg t.d.s. was most effective, 30mg o.n. was probably the best compromise in terms of efficacy and tolerability. 8 references. (Journal abstract modified)

003622 Greenway, Frank L.; Dahms, William T.; Bray, George A. Harbor General Hospital, Box 16, 1000 West Carson Street, Torrance, CA 90509 **Phenytoin as a treatment of obesity associated with compulsive eating.** Current Therapeutic Research. 21(3):338-342, 1977.

The effect of phenytoin as a treatment for obesity associated with compulsive eating is discussed. Of a group of 98 obese subjects given a questionnaire to detect compulsive eating behavior, 7 subjects were selected, 4 of whom remained for the duration of the experiment. In a double-blind study, patients were given a weight reduction diet and gelatin capsules containing either lactose (placebo) or phenytoin for 8 wk, then, after a 2 wk period with no pill, given the opposite type pill for a second 8 wk period. There was no significant difference in experienced hunger or weight loss, and no change in depression, anxiety, and hostility as revealed in the behavior questionnaire. It is concluded that phenytoin is no more effective than placebo in treating obese compulsive eaters, and even though the patients claimed to feel less hungry when taking a capsule 3 times a day in conjunction with a weight loss diet than when not taking a pill. 6 references.

003623 Hanlon, Thomas E.; McCabe, O. Lee; Savage, Charles; Kurland, Albert A. Maryland Psychiatric Research Center, Baltimore, MD 21228 **Narcotic antagonist treatment of addict parolees -- the failure of an effective approach.** Comprehensive Psychiatry. 18(3):211-219, 1977.

The results of a controlled study of the contingent administration of naloxone to newly released addict parolees were viewed in relation to the goals of the narcotic antagonist approach to the treatment of addiction. Program participation and narcotic usage data on 97 addict parolees, 55 of whom were assigned to naloxone and 42 to placebo, revealed that although demonstrating a capacity to attenuate narcotic drug intake, the use of naloxone in contingent dosages ranging from 500 to 2000mg was associated with a relatively high dropout rate during a prescribed 6 month treatment course. In view of the population and methodology employed, the unfavorable

outcome result could not be regarded as discounting the potential usefulness of naloxone in other settings. Implications of the findings, including a surprising amount of placebo effectiveness under contingent conditions, were discussed. 12 references.

003624 Hirsch, Madelyn J.; Growdon, John H.; Wurtman, Richard J. no address **Oral choline administration to patients with tardive dyskinesia.** Neurology. 27(4):391, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the effects of oral choline chloride on 18 patients with tardive dyskinesia were studied in a double-blind crossover study. The patients had chronic buccal lingual dyskinesia; 13 were schizophrenic and 5 had Alzheimer disease. The mean fasting choline level rose 174% during choline ingestion. The buccal lingual movements were greatly suppressed in 4 and moderately reduced in 4 other patients; tongue movements increased in 1 patient and dyskinetic movements were unchanged in 9 patients. No changes were detected during placebo administration. The results suggest that oral choline increases the delivery of choline and facilitates acetylcholine synthesis in human brain, and that chronic treatment suppresses buccal lingual dyskinesia in some patients.

003625 Itil, T. M.; Polvan, N.; Engin, L.; Guthrie, M. B.; Huque, M. F. Division of Biological Psychiatry, Dept. of Psychiatry, New York Medical College, New York, NY **Fluotracen (SKF-28175), a new thymo-neuroleptic with rapid action and long-acting properties (quantitative pharmaco-EEG and clinical trials in the development of fluotracen (SKF-28175)).** Current Therapeutic Research. 21(3):343-360, 1977.

Fluotracen (SKF-28175), a thymoneuroleptic drug with rapid action and long-acting properties and pharmacological properties of both antidepressants and neuroleptics, was described. Open pilot trials showed antipsychotic effects in schizophrenic patients and antidepressant effects in depressed patients based on three quantitative pharmacoelectroencephalogram studies in humans. It was established that fluotracen had significant central nervous system effects with longer duration than is common with other drugs. The onset of antidepressant effects was early (within 2 to 3 days), and one dosage daily at bedtime was enough for the treatment. Except for sedation and occasional heartburn, none of the side-effects noted with classical antidepressants and neuroleptics were observed. 8 references. (Author abstract modified)

003626 Jovanovic, U. J. no address **Polygraphic sleep recordings before and after the administration of flunitrazepam.** Journal of International Medical Research (Northampton). 5(2):77-84, 1977.

In an investigation of the psychotropic drug flunitrazepam, 10 patients aged 22 to 40-years-old, who suffered from irregular disturbances in falling asleep and in sleeping continuously, were examined over a period of 10 consecutive nights by means of polygraphic sleep recordings, neurologic psychologic investigation, and questionnaires on subjective feelings. Placebo was given for three evenings, and then 2mg of flunitrazepam for three nights, followed by placebo for three remaining nights. Results show that the flunitrazepam significantly reduced the latency times until the patients fell asleep and up to the first deep sleep. Also, the frequency of nocturnal awakenings was lessened and disturbances in sleeping continuously disappeared for the duration of treatment. Duration of wakefulness after having woken during the night also decreased considerably. Based on the findings that the patients fell asleep quickly, nocturnal awakenings were reduced, duration of wakefulness decreased, and deep sleep was prolonged, it is concluded that this preparation can be regarded as a further development in the search for a better hypnotic. 22 references. (Author abstract modified)

003627 Kark, R. A. Pieter; Blass, John P.; Spence, M. Anne. Reed Neurological Research Center, UCLA School of Medicine, Los Angeles, CA 90024 **Physostigmine in familial ataxias.** Neurology. 27(1);70-72, 1977.

Physostigmine was given to 12 patients with various spinocerebellar degenerations, and neurologic examinations were recorded on video tapes and assessed on a semiquantitative scale. Forty minutes after a single dose, the scores improved by 35.7plus or minus 4.7% (means plus or minus SEM). Eight patients were then studied over sequential 3 month periods by a randomized double-blind trial of physostigmine versus placebo. With physostigmine, scores were 33.9plus or minus 8.3% better than before treatment or with placebo. Further investigations of cholinergic drugs seem warranted in patients with these diseases. 10 references. (Author abstract)

003628 Koranyi, E. K. Ottawa General Hospital, Ottawa, Ontario, Canada **Remarkable etiology in Gilles de la Tourette's disease.** Journal of the University of Ottawa (Ottawa). 1:507, 1977.

The case history of a 16-year-old boy with Gilles de la Tourette's disease suggests that the patient's self-discovered addiction (at age 10) to inhaling gasoline up to 10 times a day was an etiological factor in the disease. The patient developed facial tics along with grunting noises and coprolalia after 1 month of gasoline inhaling. A scalp EEG revealed excessive, diffuse slow theta waves and bursts of bilateral theta activity, as well as poor regularity of alpha waves. There was evidence for both cortical and subcortical electrical dysfunctin. His overall maturity was approximately age adequate. On a daily dose of 4mg haloperidol the patient was at first controlled, but after a few weeks he deteriorated again and throughout this time complained of dizziness. He was given 7.5mg clorazepate dipotassium 3 times daily, which resulted in immediate improvement. Remission was maintained, declining only once to a mild degree when his medication ran out.

003629 Lafrance, Richard; Griggs, Robert; Moxley, Richard; McQuillen, James. no address **Hereditary paroxysmal ataxia responsive to acetazolamide.** Neurology. 27(4):370, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, acetazolamide treatment was studied in a kindred in which 9 members were afflicted with paroxysmal ataxia associated with dysarthria, incoordination, and nystagmus. Plasma amino acids, lactate and pyruvate metabolism, uric acid, and electroencephalography showed no diagnostic abnormalities during attack free intervals. No gross abnormalities of amino acid, lactate, or pyruvate concentration occurred during an attack. Prior to evaluation, a diagnosis of periodic paralysis was suspected and the proband was treated with acetazolamide, resulting in complete abolition of attacks. Subsequent evaluation showed that patients were of normal strength during attacks; provocative tests for periodic paralysis were negative. Other family members were treated and acetazolamide was effective in preventing attacks in all patients in the kindred. Substitution of placebo resulted in return of attacks in 3 to 4 days. Responses have been maintained in all patients for periods of up to 4 years. One elderly patient developed a renal calculus during therapy; no other side-effects occurred. Patients do not appear to become refractory to the beneficial effects of acetazolamide. (Author abstract modified)

003630 Lerer, Robert J.; Lerer, M. Pamela. 1277 Hicks Blvd., Fairfield, OH 45014 **Response of adolescents with minimal brain dysfunction to methylphenidate.** Journal of Learning Disabilities. 10(4):223-228, 1977.

Sixteen of 27 adolescents with minimal brain dysfunction showed subjective and objective evidence of improvement following a 60 day trial of methylphenidate (Ritalin). Positive objective changes were demonstrated in these patients by improvement in behavior as recorded by parents and teachers completing the Conners' Abbreviated Teacher Rating Scale, by improvement in performance on the Bender-Gestalt Test, and by improvement in academic achievement. Subjective improvement included increased ability to attend and to concentrate and decreased symptoms of anxiety and nervousness. No specific parameters were identified retrospectively which could have been of value in predicting which adolescents with minimal brain dysfunction were more likely to exhibit positive responses to methylphenidate therapy. These findings demonstrate that a trial of methylphenidate therapy may prove helpful for underachieving adolescents with a documented history of hyperactivity. 12 references. (Journal abstract)

003631 Lhermitte, F.; Rosa, A.; Comoy, E. Clinique de Neurologie et de Neuropsychologie, Hopital de la Salpetriere, 47 Boulevard de l'Hopital, F-75634 Paris **/Abnormal movements in Parkinsonians treated with L-dopa, and abnormalities in the dopamine metabolism./** Mouvements anormaux des Parkinsoniens traites par la L-dopa et anomalies du metabolisme de la dopamine. Revue Neurologique (Paris). 133(1):3-11, 1977.

Biochemical analyses were conducted in 28 patients with Parkinson's disease who had been treated with L-dopa. Twenty patients showed either no abnormal movements at all, or very few; eight others had considerable dyskinesia. Biochemical analysis of urinary degradation products of L-dopa revealed a significant shift in the degradation of dopamine toward 4-o-methylate derivatives in dyskinetic patients. Results are in agreement with those obtained in the initial analysis in 1973. Abnormal movements while under L-dopa treatment are dependent on two factors: hypersensitivity of dopaminergic reception, and greater or lesser preponderance of COMT (catechol-o-methyltransferase) isozyme, giving rise to 4-o-methylates. 13 references. (Journal abstract modified)

003632 Mathew, Ninan T. no address **Clinical subtypes of cluster headache and their response to lithium therapy.** Neurology. 27(4):338, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the responses to lithium therapy of 2 clinical subtypes of cluster headache: 1) episodic, with months or years of headache free intervals; and 2) chronic without significant headache free intervals, were studied. Lithium carbonate elicited marked improvement in almost 80% of chronic cluster headache patients, but the improvement in the episodic type was less marked, although lithium appeared to shorten the cluster period. Tremulousness, lethargy, nausea, and mild diarrhea were the usual side-effects. Some patients obtained total relief of headache, with persistence of autonomic symptoms like watering from the eye. The majority of chronic cluster patients were men, and all had autonomic symptoms accompanying the headache. The results indicate that lithium carbonate is the medication of choice in chronic cluster headache.

003633 McNutt, Barbara A.; Boileau, Richard A.; Cohen, Miye N. Institute for Child Behavior and Development, University of Illinois at Urbana-Champaign, IL 61801 **The effects of long-term stimulant medication on the growth and body composition of hyperactive children.** Psychopharmacology Bulletin. 13(2):36-38, 1977.

In a paper presented to a meeting to the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the effects of long-term stimulant medication (methylphenidate) on the growth and body composition of hyperactive children were studied. The study was divided into two segments, a 12 month period (a child was considered medicated if he were on the drug for 8 months or more during the period), and a 24 month period (medicated if 16 or more months out of 24); the 24 month period children were included in the 12 month group for analytic purposes. The 12 month group contained 28 medicated hyperactive children, 24 nonmedicated hyperactive children and 47 normal controls; the 24 month group contained 13 medicated hyperactive, 10 nonmedicated hyperactive and 14 normal controls. The hyperactive children on methylphenidate grew at the same rate as the control children over both periods. Over the 12 month period, the hyperactives increased their body girth at a slower rate than the controls. During the 24 month period, the hyperactives tended to add more fat weight than the controls. There were no significant differences in growth or body composition changes between the medicated and nonmedicated hyperactives. The results indicate that for these children, methylphenidate over 1 or 2 years did not produce growth suppression. 2 references.

003634 Miceli, G.; Caltagirone, C.; Gainotti, G. Clinic for Nervous and Mental Diseases, Catholic University, Via Pineta Sacchetti 644, I-00168 Rome, Italy **Gangliosides in the treatment of mental deterioration: a double-blind comparison with placebo.** Acta Psychiatrica Scandinavica (Stockholm). 55(2):102-110, 1977.

Thirty patients showing signs of mental deterioration were submitted to a neuropsychological battery before and after treatment with gangliosides, and their performances were compared, in a double-blind study, with those obtained on the same tests by 30 patients affected by similar degrees of dementia and treated with placebo. The improvement shown on Raven's Colored Progressive Matrices and on Immediate Visual Memory by the active group was significantly higher than that shown by the placebo group. An evaluation of the overall effect of gangliosides therapy showed a highly significant difference between the active and placebo group, still in favor of the subjects treated with gangliosides. It is concluded that gangliosides may exert a positive effect in the treatment of demential syndromes. 13 references. (Journal abstract)

003635 Morgan, Marsha Y.; Jakobovits, Andrew; Elithorn, Alick; James, Ian M.; Sherlock, Sheila. Dept. of Medicine and Psychiatry, Royal Free Hospital School of Medicine (University of London), London NW3 2QG, England **Successful use of bromocriptine in the treatment of a patient with chronic portasystemic encephalopathy.** New England Journal of Medicine. 296(14):793-794, 1977.

A case of successful use of bromocriptine in the treatment of a patient with chronic portasystemic encephalopathy is reported. Under bromocriptine treatment, the patient became alert, his recent memory improved, and his speech and gait abnormalities disappeared. A rapid deterioration in his condition occurred within 5 days of a change to placebo. When bromocriptine was reintroduced an improvement was seen within 7 days. No side-effects from the drug were experienced. The concept that chronic portasystemic encephalopathy may, at least in part, be explained by a defect in dopaminergic neurotransmission is suggested. 11 references.

003636 Murphy, J. E. no address **A comparative trial of Anafranil, Pertofran and an Anafranil/Pertofran combination.** Journal of International Medical Research (Northampton). 5(Supplement 1):16-23, 1977.

At a symposium held at Rabat, Malta, in November, 1976, two antidepressants, Anafranil (clomipramine) and Pertofran (desipramine) were compared in the management of depression in general practice, and a further comparison was made to ascertain whether a combination of the two antidepressants was more effective than the drugs given alone. One hundred and seventy three patients were admitted to a double-blind clinical trial, conducted on a multicenter basis in general practice, in which a double dummy technique was employed. One hundred and forty one patients completed the study. Of these, 49 received Anafranil, 49 received Pertofran and 43 the combination. Although there were no statistically significant differences between the three treatment regimes, there was a consistent trend in favor of the combination regime. Ninety one percent of the patients who completed treatment on the combination showed satisfactory improvement compared with 81% on the Anafranil regime and 78% on Pertofran. An attempt was made to identify three symptom clusters -- anxiety, anergia, and biological depression. There was no significant difference in the response of these three clusters to the three treatment regimes, nor was there any difference in the incidence and severity of side-effects. (Journal abstract)

003637 Nahas, Abbas D.; Krynicki, Victor. Queens Children's Psychiatric Center, Bellerose, NY 11426 **Effect of methylphenidate on sleep stages and ultradian rhythms in hyperactive children.** Journal of Nervous and Mental Disease. 164(1):66-69, 1977.

The effect of methylphenidate on sleep stages and ultradian rhythms was studied in 4 hyperactive children. Two nights of sleep were recorded before drug administration. Sleep was again recorded on the 1st and 21st nights during drug administration, and also on the 1st and 2nd nights of drug withdrawal. All patients showed behavioral improvement during drug administration; however, no drug effect was seen when standard sleep variables such as sleep stages and sleep time were examined. This analysis was supplemented by an examination of the rapid eye movement cycle and computer extraction of the delta cycle; both are ultradian (40 to 140 minutes) rhythms. These rhythms were found to be intact in hyperactive patients. Although the REM cycle was not affected by drug administration or withdrawal, a trend toward lengthening of the delta cycle was found on drug withdrawal. 8 references. (Author abstract modified)

003638 Osborn, Gerald G.; York, Jonathan L. Department of Psychiatry, Michigan State University, East Lansing, MI 48823 **Psychoactive drugs in the treatment of the aged.** Practical Psychology for Physicians. 4(4):20-25 28-29, 1977.

The use of psychoactive drugs in the treatment of the aged is discussed, and seen as indicated only after various types of environmental engineering have been employed to obtain the desired effects. Three common vasodilators (papaverine, cyclandelate, and dihydrogenated ergot alkaloids) and their mechanism of action are described. Before starting a patient on psychotropic medications, it is suggested that the physician make sure that he already has a reasonable diet and sufficient exercise and recreation, and make sure that a vasodilator cannot be used to achieve the desired effect. Indications and side-effects of the major psychoactive drugs are discussed.

003639 Pena-Ramos, Abelardo. Psychiatry Service, Veterans Administration Hospital, 13000 North 30th Street, Tampa, FL 33612 **Thioridazine HCl vs. chlordiazepoxide HCl in controlling symptoms attributable to alcohol withdrawal.** Diseases of the Nervous System. 38(3):144-147, 1977.

Thioridazine HCl or chlordiazepoxide HCl was administered to 58 adult patients over a 4 week biochemical and psychological testing period to compare the relative efficiency of these drugs in controlling symptoms attributable to alcohol withdrawal. Physiological observations at the beginning and end of the study included: blood cell count, differential, hematocrit, urinalysis, and ECG. Psychological testing included three inventories (the Hamilton Psychiatric Rating Scale for Depression, the Zung Self-Rating Scale for Depression, and the Lipman Self-Rating Symptoms Scale). The results of statistical analysis suggested that: 1) thioridazine is as efficacious as chlordiazepoxide in controlling symptoms attributable to alcohol withdrawal; 2) thioridazine is as safe as chlordiazepoxide; and 3) thioridazine is superior to chlordiazepoxide in relieving the depressive elements of the alcohol withdrawal state and in the further recovery period. The conclusions suggest strong support for thioridazine as a therapeutic agent for the depressed alcoholic patient who is a high suicidal risk. 11 references.

003640 Penovich, Patricia; Griggs, Robert C.; Moxley, Richard T.; Charlton, Maurice H. no address **Hypersomnia in myotonic dystrophy: treatment with methylphenidate.** Neurology. 27(4):403, 1977.

At a meeting of the american Academy of Neurology in Atlanta, GA in April, 1977, nine patients with severe hypersomnia in myotonic dystrophy were treated in a double-blind crossover study with methylphenidate (MP). All night electroencephalogram (EEG) monitoring showed that the proportion of slow wave sleep and rapid eye movement sleep varied markedly and there was an increased percentage of slow wave sleep in 5; normal sleep related growth hormone release occurred in 7 but was not confined to slow wave sleep. Three week treatment with MP dramatically decreased reported lethargy, sleep requirements, and number of daily naps in 5 of 9 patients. Mood improved in 5 but no change in cognitive functioning was found. EEG and metabolic study results did not change significantly. MP remained effective for a subsequent 6 months in 7 and no side-effects occurred. The results indicate that MP offers at least short-term benefit for the hypersomnia of myotonic dystrophy. Of 49 adult patients with myotonic dystrophy evaluated for sleep disorders, 25 had excessive daily sleep (10 or more hrs/day) and in 23 hypersomnia was a major complaint. Eighteen patients had severe hypersomnia (12 or more hrs/day) none of a control group with other forms of muscular dystrophy had hypersomnia. (Author abstract modified)

003641 Ross, Michael S.; Moldofsky, Harvey. Clinical Investigation Unit, Clark Institute of Psychiatry, Toronto, Ontario M5T 1R8, Canada **Comparison of pimozide with haloperidol in Gilles de la Tourette syndrome.** Lancet (London). No. 8002:103, 1977.

In a letter to the editor, preliminary findings in a double-blind placebo controlled clinical comparison of pimozide and haloperidol in five White males with Gilles de la Tourette syndrome are reported. Both medications significantly decreased tic frequency. The drugs did not differ significantly in their dopamine receptor blocking activity. Pimozide led to significantly fewer complaints of adverse effects, particularly tiredness, and this was reflected in greater immediate and long-term patient acceptance of pimozide. 5 references.

003642 Samet, Charles M. State University of New York, Stony Brook, NY 11790 **The evaluation of Bellergal Tablets compared to Librium and placebo in the treatment of symptoms of anxiety tension states associated with functional gastrointestinal disorders.** Psychosomatics. 17(4):202-209, 1977.

A controlled, double-blind comparison of the tranquilizer Librium (chlordiazepoxide HCl) and the autonomic stabilizer Bellergal Tablets (ergotamine tartrate, bellafoline, phenobarbital) in patients experiencing anxiety/tension associated with functional gastrointestinal disorders was presented. The Ss were 75 adult patients who presented a variety of functional gastrointestinal disorders and symptoms of anxiety/tension. Patients were randomly assigned to one of three therapeutic regimens: Bellergal therapy chlordiazepoxide HCl or placebo. Efficacy of the test medications was measured by changes from the pretrial mental and physical conditions as established by the Hamilton Anxiety Rating Scale. While both Bellergal and Librium were effective in treating patients experiencing anxiety/tension associated with functional gastrointestinal disorders, both statistical and clinical trends in the data indicated that Bellergal was superior. 5 references.

003643 Sato, Susumu; Penry, J. Kiffin; Dreifuss, Fritz, E.; Dyken, Paul R. no address **Clonazepam in the treatment of absence seizures: a double-blind clinical trial** Neurology. 27(4):371, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the efficacy of clonazepam (CL) was compared with ethosuximide (ES) in the treatment of absence seizures in 79 children in a double-blind trial. Thirty patients in the CL and 33 in the ES group completed a required period of study, while 13 in the CL and 3 in the ES group did not. Drowsiness, and ataxia were common side-effects and seemed dose related. Withdrawal from CL therapy was most commonly related to behavioral changes, that is, hyperactivity, short attention span, and uninhibited and aggressive behavior, and, occasionally, to increased seizure counts. CL was an effective and potent antiabsence agent, but its effectiveness seemed transitory in some patients. (Author abstract modified)

003644 Schapira, Kurt; McClelland, Hamish A; Newell, David J. Dept. of Psychological Medicine, Royal Victoria Infirmary, Queen Victoria Rd., Newcastle Upon Tyne NE1 4LP, England **A comparison of high- and low-dose lorazepam with amylobarbitone in patients with anxiety states.** American Journal of Psychiatry. 134(1):25-28, 1977.

The efficacy of lorazepam at two dose levels was compared with that of amylobarbitone in treating patients with anxiety states in a double-blind crossover trial. A total of 40 outpatients was divided into low and high dose lorazepam groups. Lorazepam was administered in doses of 0.75mg three times daily for 7 days followed by 65mg amylobarbitone three times daily for 7 days, or 65mg three times daily for 7 days followed by 0.75mg amylobarbitone three times daily for 7 days. Results reveal the effective anxiolytic action of lorazepam. Evaluation of the patients' responses during each week of treatment was based on a physician's weekly rating and on daily self-rating by patients. The results were analyzed by sequential and nonsequential analyses. The main side-effect of the drug was drowsiness, which occurred to a clinically significant degree among the high dose group of patients. The value of having two dosage trials, particularly in devising subsequent flexible individual treatment regimens, is emphasized. 10 references. (Author abstract modified)

003645 Seimeon, Jovan; Gross, Meir; Mueller, Jane. Department of Psychiatry, University of Ottawa, Ottawa, Ontario, Canada **Neuroleptic drug effects on children's body weight and height.** Psychopharmacology Bulletin. 13(2):50-53, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, changes in bodyweight and height were studied in 15 hospitalized psychotic boys during neuroleptic drug therapy with thiothixene, fluphenazine, or haloperidol, and following drug withdrawal. During neuroleptic drug therapy, as well as during placebo administration following drug withdrawal, the patients received trihexylphenidyl daily. There were positive correlations between weight gain and the total amount of all three neuroleptic drugs; following drug withdrawal, there was a negative correlation. Six boys who had received medication for a mean of 71 weeks showed an acceleration of growth in height; five who had received medication for a mean of 39 weeks remained in the same percentile as on admission, and two boys on medication for less than 11 weeks showed no growth changes. The reported effects of psychotropic drugs on growth in height, if confirmed, may result from changes in food intake, growth hormone secretions due to alterations of the duration or depth of sleep, or gonadotrophic hormones. 4 references.

003646 Tunks, Eldon R.; Dermer, Stanley W. Hamilton Psychiatric Hospital, West 5th Street, Hamilton, Ontario, L9C 3N6, Canada **Carbamazepine in the dyscontrol syndrome associated with limbic system dysfunction.** Journal of Nervous and Mental Disease. 164(1):56-63, 1977.

The use of carbamazepine in the dyscontrol syndrome associated with limbic system dysfunction is discussed. There has been a demonstrated association between certain behavioral problems and EEG abnormalities, particularly the association of aggressive and sometimes violent behavior with foci in the temporal lobes. The concept of dyscontrol syndromes has also been established and it is possible that some instances of the dyscontrol syndrome arise from an abnormal sensitization of the limbic system due to disturbance in or near the temporal lobes. Carbamazepine is a drug, with both anticonvulsant and psychotropic properties for which both the behavioral effects and pharmacological actions have been defined. The properties of carbamazepine for blocking polysynaptic reflexes and suppressing posttetanic potentiation are discussed with respect to this limbic system dysfunction in the dyscontrol syndrome. It is also proposed that this drug might be considered for its psychotropic effect in certain instances of dyscontrol, with or without clinical diagnosis of epilepsy. An illustrative case is cited. 47 references. (Author abstract modified)

003647 Walinder, Jan; Wallin, Lief; Carlsson, Arvid. S-422 03 Hisings Backa 3, Sweden **Effect of baclofen on cerebrospinal-fluid levels of 5-hydroxyindoleacetic acid and homovanillic acid.** New England Journal of Medicine. 296(8):452-453, 1977.

To determine the effect of baclofen, a gamma-aminobutyric acid derivative, on the cerebrospinal fluid levels (CSF) of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA), three schizophrenics, two paranoid psychotics, two alcohol induced dementia patients, and one manic-depressive were administered a daily dose of baclofen for 4 weeks in addition to their normal medication. CSF assays for 5-HIAA and HVA were done before and after the experimental period. In general, no significant differences were found in posttreatment values of 5-HIAA, HVA or 4-hydroxy-3-metoxy-phenylglycol nor were any changes in mental function observed. Findings

suggest that no profound changes in serotonin or catecholamine metabolism as reflected in CSF levels occurred. 8 references.

003648 Walker, Barry R.; Ballard, Ian M.; Gold, Jerome A. Wyeth Laboratories, P.O. Box 8299, Philadelphia, PA 19101 **A multicentre study comparing mazindol and placebo in obese patients.** Journal of International Medical Research (Northampton). 5(2):85-90, 1977.

To define the potential of the drug mazindol for causing weight loss, a 6 week double blind placebo controlled study involving 245 obese patients at four centers was undertaken. Results show no significant clinical or laboratory abnormalities occurring from mazindol therapy. The mazindol therapy group without behavioral modification and behavioral modification alone both resulted in a statistically significant mean weight loss of one pound/patient/week and mazindol plus behavioral modification resulted in a greater mean weight loss of one half pound/patient/week than with behavioral modification alone. The placebo group did not lose weight without behavioral modification and had a higher drop out rate compared to the mazindol therapy group. It is concluded that mazindol which has not shown side effects or abuse potential is of value in the initial therapy of obesity. 10 references. (Author abstract modified)

003649 Werry, J. S.; Aman, M. G.; Dowrick, P.; Lampen, E. L. Department of Psychiatry, School of Medicine, University of Auckland, P.G., Auckland, New Zealand **Imipramine and chlordiazepoxide in enuresis.** Psychopharmacology Bulletin. 13(2):38-39, 1977.

In a paper presented to a meeting of the Early Clinical Drug Evaluation Units (ECDEU) of NIMH, at Key Biscayne, FL, in May 1976, the immediate (after 3 days) and short-term (after 3 weeks) effects of imipramine (IM) and chlordiazepoxide (CZ) in manufacturers' recommended doses for enuresis were studied in a double-blind crossover study of 20 children. The drugs were given in the following order: IM, placebo, and CZ, and vice versa. IM (25 or 50mg) decreased the frequency of wetting by 25%, increased heartrate by 6 beats per min, and caused a slight weight loss. It may have slightly impaired motor coordination of the hand. CZ was ineffective in the doses used (5 or 10mg). IM increased psychosomatic complaints and CZ decreased them very slightly. There were no changes in cognitive function, although IM reduced extraneous seat movement during both the Continuous Performance Test and the Short Term Memory test. The results indicate that imipramine can have a variable symptomatic effect upon bedwetting that is accompanied by a stimulant type activity, but that the manufacturers' recommended dose of chlordiazepoxide is too low and without any pharmacological effect in the majority of children. 1 reference.

003650 Westblom, Ulf. Oskarshamn Hospital, Oskarshamn, Sweden **Stiff-man syndrome and clonazepam.** Journal of the American Medical Association. 237(18):1930, 1977.

A case report of a 55-year-old diabetic woman who suffered from stiff-man syndrome and who was successfully treated with the new benzodiazepine derivative, clonazepam, is presented. The stiff-man syndrome was first described in 1956, as a disease characterized by progressive fluctuating muscular rigidity and spasm, and by now, more than 50 cases have been documented. Diazepam in high dosages, usually around 40 to 60mg/day, has been the only known treatment, with considerable relief of symptoms in a majority of cases. The patient was administered clonazepam as she was gradually withdrawn from the high dosages of diazepam which she had been receiving. 3 references.

003651 Wolf, Sheldon M.; Carr, Andrew; Davis, David C.; Davidson, Sherwood; Dale, Earle P.; Forsythe, Alan; Goldenberg, Erwin D.; Hanson, Rebecca 1526 North Edgemont St., Los Angeles, CA 90027 **The value of phenobarbital in the child who has had a single febrile seizure: a controlled prospective study.** Pediatrics. 59(3):378-385, 1977.

A study was undertaken to investigate the effects of phenobarbital in the child who has had a single febrile seizure, and to compare drug regimens and side-effects. There was no significant difference in the recurrence rate between children receiving intermittent as compared with no phenobarbital. The recurrence rate in children receiving daily phenobarbital was significantly decreased compared to either of the other two groups. Severe recurrent febrile seizures occurred in no children on daily phenobarbital and in 4.4% of the children receiving either intermittent or no phenobarbital. Parental resistance, compliance, and reversible hyperactivity were the main problems encountered with the continuous phenobarbital regimen. 24 references.

003652 Yepes, L. E.; Balka, Elinor B.; Winsberg, Bertrand G.; Bialer, Irv. Child Psychiatric Evaluation Research Unit, 524 Clarkson Ave., Brooklyn, NY 11203 **Amitriptyline and methylphenidate treatment of behaviorally disordered children.** Journal of Child Psychology and Psychiatry, etc. (Oxford). 18(1):39-52, 1977.

To assess the controlled, relative effectiveness of amitriptyline and methylphenidate for treating hyperactive/aggressive behavior in children originally referred to a learning clinic, behavioral change was measured through parent and teacher ratings. Drug effects on attention, short-term memory, and impulsivity were evaluated with laboratory tasks. It was found that both drugs were largely comparable in attenuating hyperactivity and aggression. Of the laboratory measures, only attention was improved by both drugs. With the exception of amitriptyline induced sedation, side-effects were of minor degree. Findings raised questions concerning measuring and improving attentiveness. Differences between results of this and other studies were discussed, as were issues regarding pharmacotherapy with amitriptyline in children. 35 references. (Author abstract)

13 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

003653 Alfredsson, Gunnel; Wiesel, Frits-Axel; Fyro, Bengt; Sedvall, Goran. Dept. of Psychiatry, Karolinska Institutet, S-10401 Stockholm, Sweden **Mass fragmentographic analysis of clomipramine and its mono-demethylated metabolite in human plasma.** Psychopharmacology (Berlin). 52(1):25-30, 1977.

A newly developed mass fragmentographic method for the quantification of clomipramine (CIM) and monodemethylclomipramine (CIM) in human plasma is described. The deuterium labeled analogues of the compounds are used as internal standards. The method was applied to the analysis of drug concentrations in plasma of five clomipramine treated healthy volunteers and five depressed patients. After administration of a single oral 25mg dose to the healthy volunteers, the maximum level of CIM plasma was reached about 3 h after administration. The average half-life for the elimination of CIM from plasma was calculated, assuming a two compartment model, to be about 12 h. DCIM levels were always much lower than those of CIM and in same samples were undetecta-

ble. In patients receiving chronic administration of the drug (100mg/day), plasma levels of CIM and DCIM showed great individual differences. The ratio between CIM and DCIM was nearly constant for each individual, suggesting that the metabolism of CIM may be determined genetically. In three patients, the DCIM level exceeded that of CIM. Possible explanations for the results are discussed. 12 references. (Author abstract modified)

003654 Asberg, Marie; Ringberger, Vivi-Ann; Sjoqvist, Folke; Thoren, Peter; Traskman, Lil; Tuck, J. Richard. Department of Clinical Pharmacology, Huddinge University Hospital, S-141 86 Huddinge, Sweden. **Monoamine metabolites in cerebrospinal fluid and serotonin uptake inhibition during treatment with chlorimipramine.** Clinical Pharmacology and Therapeutics. 21(2):201-207, 1977.

The effects of chlorimipramine on the concentrations of the main metabolites of serotonin 5-hydroxtryptamine (5-HT), norepinephrine (NE) and dopamine, e.e.,5-hydroxyindoleacetic acid (5-HIAA), 4-hydroxy-3-methoxyphenlglycol (HMPG), and homovanillic acid (HVA), respectively, were studied in cerebrospinal fluid (CSF) from 14 depressed patients. These effects were related to the 5-HT uptake inhibiting activity and NE uptake inhibiting activity in vitro of plasma drawn from the patients. Chlorimipramine inhibited the uptake of both transmitter amines in all patients. During treatment, the levels of 5-HIAA and HMPG in CSF were significantly reduced. HVA levels were reduced in 6 patients and increased in 8 patients; there was no mean change. The decrease in 5-HIAA level in CSF was correlated to the uptake inhibition of 5-HT but there was no corresponding relationship between NE uptake and HMPG levels. The changes in HVA levels were also correlated to the uptake of 5-HT despite the absence of a unidirectional change of this metabolite. 31 references. (Author abstract modified)

003655 Axelsson, Rolf; Martensson, Erik. Department of Psychiatry III, Lillhagen's Hospital, S-42204 Hisings Backa, Sweden **The concentration pattern of nonconjugated thioridazine metabolites in serum by thioridazine treatment and its relationship to physiological and clinical variables.** Current Therapeutic Research. 21(4):561-586, 1977.

The serum concentrations of thioridazine and its main nonconjugated metabolites -- thioridazine side-chain sulfoxide, thioridazine side-chain sulfone and thioridazine ring sulfoxide -- were determined in a single dose study. The serum concentrations of the same substances were also determined in groups of thioridazine treated patients, all together 240, and the metabolite pattern was examined for any variation with physiological and clinical variables for the relation, if any. Gas chromatography was used for the determinations and a nonparametric method of partial correlation analyses was used in the statistical analyses. As a whole, variation of the side-chain oxidation products with different physiological and clinical variables was rather limited, while the ring sulfoxide was conspicuous. 12 references. (Author abstract)

003656 Baker, Gordon A.; Santalo, Roberto; Blumenstein, Jan. Department of Research and Department of Psychiatry, Mount Sinai Hospital, Toronto, Canda **Effect of psychotropic agents upon the blastogenic response of human T-lymphocytes.** Biological Psychiatry. 12(2):159-169, 1977.

Experiments examining the effects of psychotropic drugs in vitro, upon the blastogenic response of the T-lymphocyte with the aim of elucidating the intracellular mechanisms of these agents are described. Antischizophrenic agents, phenothiazine and nonphenothiazine, were found to inhibit the transformation of the T-lymphocyte in vitro. This inhibition occurs only in the early event and is neither competitive with dopamine, nor appears to involve Na+/K+ adenosine triphosphatase. RNA synthesis is more sensitive to the inhibitory effect than DNA or protein synthesis. This leads to the conclusion that chlorpromazine may act by inhibiting the synthesis of newly formed RNA, and subsequently, transformation, rather than by alteration of the cell membrane. 18 references. (Author abstract modified)

003657 Beaumont, G. Research and Medical Department, CIBA-GEIGY (UK) Limited, Macclesfield, England **An investigation into the short-term effects of clomipramine (Anafranil) administered in low doses, on weight.** Journal or International Medical Research (Northampton). 5(Supplement 1):32-36. 1977.

At a symposium held at Rabat, Malta, in November, 1976, the short-term effects of clomipramine administered in low doses, on body weight change was investigated. Patients treated with four dosage regimes of clomipramine 10mg t.d.s.,30mg o.n.,25mg t.d.s. and 75mg o.n. in a clinical trial lasting four weeks were regularly weighed. Due allowance was made for the normality or otherwise of normal weight, appetite and, in women, menstruation. There was no evidence that during the four weeks of this particular study and on these doses of clomipramine patients showed any increase in weight. (Journal abstract modified)

003658 Becker, Robert E.; Shaskan, Edward G. Hall-Brooke Hospital, Westport, CT 06800 **Platelet monoamine oxidase activity in schizophrenic patients.** American Journal of Psychiatry. 134(5):512-517, 1977.

Platelet monoamine oxidase (MAO) activity was studied in 29 schizophrenic inpatients and 26 schizophrenic outpatients during a 4 week double-blind trial of chlorpromazine with imipramine or thiothixene with placebo. Significantly more schizophrenic patients than normal control subjects had low platelet MAO activity after four weeks. Outpatients with low MAO activity were distinguished by increasing behavioral activity and reduced social apathy. Inpatients with low MAO activity were distinguished by severity of illness and symptoms. Hallucinations were significantly more frequent among patients with low MAO activity. It is suggested that platelet MAO activity might decline in some actively schizophrenic patients as part of the psychotic process. 35 references. (Author abstract modified)

003659 Bigger, J. Thomas, Jr.; Kantor, Shepard J.; Glassman, Alexander H.; Perel, James M. College of Physicians and Surgeons, Columbia University, NY **Is physostigmine effective for cardiac toxicity of tricyclic antidepressant drugs?** Journal of the American Medical Association. 237(13):1311, 1977.

In a letter to the editor, the use of physostigmine for cardiac dysfunctions due to tricyclic antidepressants is questioned. The previously reported efficacy of physostigmine in a case of cardiac toxicity due to tricyclic antidepressant poisoning is not considered the result of action on intraventricular conduction or ventricular arrhythmias but rather to drug elimination. The contention is based on the poor cholinergic innervation of the ventricles and the long lag between drug administration and cardiac effect. Physostigmine does, however, have a role in cardiotoxicity, which role should be clearly defined since use of the drug also presents some hazards. 5 references.

003660 Boyar, Robert M.; Hellman, Leon D.; Roffwarg, Howard; Katz, Jack; Zumoff, Barnett, O'Connor, John; Bradlow, H. Leon; Fukushima, David K. Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, TX 75235 **Cortisol secretion and metabolism in anorexia nervosa.** New England Journal of Medicine. 296(4):190-193, 1977.

Cortisol secretion and metabolism was studied in 10 women with anorexia nervosa. The 24 hour mean plasma cortisol concentration was 8.9micrograms per deciliter (controls, 4.9). Secretory patterns showed normal circadian rhythms. Cortisol half-life was prolonged from 60 to 78 minutes, and metabolic clearance rate was decreased from 359 to 177 liters per day. Cortisol production was normal. Urinary cortisol was slightly elevated in two of five patients. These findings, as well as the increased tetrahydrocortisol/tetrahydrocortisone ratio, also appear in hypothyroid patients. Thyroid function studies showed normal total and free thyroxine and thyrotropin, but low plasma triiodothyronine levels. In five additional patients with anorexia nervosa studied before and after short-term triiodothyronine administration, metabolic abnormalities decreased as plasma triiodothyronine levels rose to or above normal. 32 references. (Author abstract)

003661 Caine, Eric D.; Kartzinel, Ronald; Ebert, Michael H.; Carter, Anne C. no address **Dopaminergic regulation of prolactin release in patients with Huntington disease and normal controls.** Neurology. 27(4):392, 1977.

Dopaminergic regulation of prolactin release was studied in 8 normal At a meeting of the American Academy of Neurology in Atlanta, Ga in April, 1977, dopaminergic regulation of prolactin release was studied in 8 normal subjects and 7 patients with Huntington disease. Plasma prolactin levels were measured from 30 min before until 360 min after the oral administration of placebo, chlorpromazine, carbidopa followed by levodopa, or bromocriptine. After placebo, Huntington disease patients had significantly higher prolactin levels than normal subjects at all times except 180, 240, and 360 minutes. When compared with their own placebo values, normal subjects showed a significant suppression of prolactin release at 180 and 240 minutes after carbidopa/levodopa and at 180, 240, and 360 minutes after bromocriptine. In contrast, Huntington disease patients demonstrated no change after both carbidopa/levodopa and bromocriptine. Both groups showed a sustained elevation after chlorpromazine. In spite of having an initially higher baseline, the prolactin levels of Huntington disease patients were significantly less than those of normal subjects at 180 and 240 minutes. These data suggest that Huntington disease patients have a less sensitive dopaminergic system for the control of prolactin release. (Author abstract modified)

003662 Carrigan, P. J.; Chao, G. C.; Barker, W. M.; Hoffman, D. J.; Chun, A. H. C. Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064 **Steady-state bioavailability of two clorazepate dipotassium dosage forms.** Journal of Clinical Pharmacology. 17(1):18-28, 1977.

The bioavailability of clorazepate dipotassium after administration of a newly developed 22.5mg tablet intended for once daily administration was compared with the bioavailability of the drug administered as three 7.5mg capsules once daily or as one 7.5mg capsule given every 6 hours. Peak serum levels from the tablet were intermediate between those of the single dose and divided dose capsules regimens. The extent of absorption was not affected. The serum half-life of nordiazepam, the major metabolite present in serum, was about 48 hours. Administration of the tablet and the multiple dose capsule regimen for 10 days indicated that each dosage form yielded similar minimum steady state serum levels which plateaued after 7 days of administration. The serum half-life of nordiazepam following 14 days of administration was similar to that found after a single dose. It is concluded that the 22.5mg tablet administered once daily produces serum levels equivalent to those achieved by administration of one 7.5mg capsule every 6 hr. 10 references.

003663 Coppen, Alec; Wood, Keith. M.R.C. Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey KT19 8PB, England **Total and non-bound plasma-tryptophan in depressive illness.** Lancet (London). No. 8002:94, 1977.

In a letter to the editor, a study is reported in which patients with primary depressive illness and no history of mania were assessed for severity of depression by the first 16 items of the Hamilton rating scale before and after treatment with amitriptyline (150mg daily) for 6 weeks. No significant difference could be found in the concentration of total plasma tryptophan between males and females in neither patients nor controls. There was no correlation between age and plasma concentration of total tryptophan. These results do not support those of Riley and Shaw, however, the differences may be attributed to the fact that the study was confined to one drug, amitriptyline, and to one sex and was performed on large numbers. 3 references.

003664 Dahl, Svein G.; Strandjord, Roald E. Institute of Medical Biology, University of Tromso, N-9001 Tromso, Norway **Pharmacokinetics of chlorpromazine after single and chronic dosage.** Clinical Pharmacology and Therapeutics. 21(4):437-448, 1977.

Plasma concentrations of chlorpromazine and its sulfoxide were measured after single intramuscular, single oral, and multiple oral doses of chlorpromazine. In four of nine patients, intramuscular doses gave stable chlorpromazine plasma levels which were maintained for 12 hr or longer. Chlorpromazine sulfoxide was found in plasma from all patients after oral doses but not after intramuscular doses, which indicates that sulfoxidation took place presystemically. The biologic availability of single oral doses relative to single intramuscular doses ranged from 10% to 69%, and was on average 32%. After 33 days of oral dosing, the plasma levels of chlorpromazine were on average 37% lower than might have been predicted from the single oral dose curves. This was not due to decreased biologic half-life of chlorpromazine, but apparently to a decrease in the biologic availability by oral administration, possibly by increased presystemic metabolism. 31 references. (Author abstract)

003665 De Fraites, Emanuel G., Jr.; Davis, Kenneth L.; Berger, Philip A. National Institute of Mental Health, Bethesda, MD 20014 **Coexisting tardive dyskinesia and parkinsonism: a case report.** Biological Psychiatry. 12(2):267-272, 1977.

A case report is presented of a pharmacological attempt to manipulate the cholinergic/dopaminergic balance in a patient with coexisting neuroleptic induced parkinsonism and tardive dyskinesia. The patient received benztropine and physostigmine challenges on successive days and the effects on both syndromes are described. The clinical course of both diseases is discussed in terms of a balance hypothesis between dopaminergic and cholinergic neurotransmission. 22 references. (Author abstract)

003666 de la Vega, C. E.; Slater, S.; Ziegler, M. G.; Lake, C. R.; Murphy, D. L. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, MD 20014 **Reduction in plasma norepinephrine during fenfluramine treatment.** Clinical Pharmacology and Therapeutics. 21(2):216-221, 1977.

The effects of fenfluramine on circulating plasma norepinephrine (NE) levels and on plasma dopamine beta-hydroxylase (DBH) activity were examined in a group of patients with affective disorders who received 120mg/day of the drug for ten days or more. Plasma NE levels were reduced to 30% of control levels and plasma DBH activity was significantly reduced. It is suggested that chronic administration of fenfluramine may induce antiadrenergic effects which may be useful in the treatment of disorders affected by circulating catecholamines. 29 references. (Author abstract modified)

003667 Dunges, W.; Schottdorf, B. Pharmakologisches Institut der Universitat Mainz, Obere Zahlbacher Str. 67, D-6500 Mainz, Germany **The determination of barbiturates in blood with glass capillary gas chromatography.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R4, 1977.

A report on the determination of barbiturates in blood with glass capillary gas chromatography, given at the 18th spring meeting of the Deutsche Pharmakologische Gesellschaft, held in Mainz, Germany in March 1977, is presented. Sensitivity and separation power are enhanced when glass capillary gas chromatography rather than packed columns is used. Using a glass capillary column, 21 of 25 N,N-dimethyl barbiturate derivatives could be separated, while with a packed column only 10 of 17 barbiturates could be separated after methylation and the detection limit was five times higher. After extraction and methylation, seven barbiturates of toxicological interest could be correctly identified in concentrations of 10 micrograms/ml from 1ml of serum. It is suggested that glass capillary gas chromatography should be useful in identifying the barbiturate involved in specific cases of barbiturate intoxication so that severity and duration of the intoxication can be predicted. (Author abstract modified)

003668 Ebstein, Richard P.; Belmaker, Robert H. Jerusalem Mental Health Center, P.O.B.140, Jerusalem, Israel **A comparison of the effect of lithium and haloperidol on human peripheral beta-adrenergic adenylate cyclase.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 27-39).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December, 1975, a study of the effects of lithium and haloperidol on epinephrine induced increases in human peripheral beta-adrenergic adenylate cyclase activity (as measured by increases in plasma cyclic adenosine monophosphate) is reported. Lithium inhibited the peripheral beta-adrenergic stimulated rise in adenylate cyclase activity, but haloperidol did not. It is suggested that this action of lithium and the results of a number of animal experiments provide a basis for a hypothesis of lithium action in mania, i.e. the hypothesis that lithium inhibits norepinephrine sensitive adenylate cyclase in the brain. The failure of haloperidol to act in this study may be related to the clinically different patterns by which haloperidol and lithium appear to control the manic phase of manic-depressive illness. 50 references.

003669 Escobar, Javier I.; Gomez, Orlando; Tuason, V. B. Tennessee Psychiatric Hospital, 865 Poplar, Memphis, TN 38105 **Depressive subtypes, blood pressure changes and response to treatment.** Diseases of the Nervous System. 38(2):76-79, 1977.

The effects of intravenous chlorimipramine on blood pressure were examined in 20 depressed patients with primary or secondary affective disorders. Patients with primary affective disorder showed a significantly greater decline in systolic blood pressure than patients with secondary affective disorder. The decline in blood pressure paralleled clinical improvement. It is suggested that differential changes in blood pressure are another instance of constitutional differences for depressive subtypes, and may prove to be practical, reliable predictors of response to tricyclic antidepressant. 11 references. (Author abstract modified)

003670 Firemark, H. M.; McIntyre, H. B.; Bodner, L.; Cho, A.; Jenden, D. no address **Amphetamine metabolism in hyperactive children.** Neurology. 27(4):400, 1977.

Amphetamine metabolism was studied in 30 hyperactive children treated in double-blind fashion with dextroamphetamine (DA), levoamphetamine (LA), or placebo (P). Approximately one fifth responded to P by parents' evaluation. Teachers' assessment demonstrated significant improvement in hyperactivity with both DA and LA. Amphetamine (A) blood levels were maximal by 3 hrs after ingestion, and the average serum half-life was 7 hrs. Saliva A concentrations were up to 8 fold greater than blood levels during the 1st few hrs and fluctuated widely, hence were not reliable for judging compliance or regulating dosage. DA and LA did not differ significantly in absorption or excretion, and there was no evidence of altered metabolism in nonresponders as compared with responders. Power spectral electroencephalograms recorded repeatedly during treatment showed no major alteration of predominant frequencies or power spectrum associated with drug, although muscle and movement artifacts were less evident during treatment with A as compared with P. (Author abstract modified)

003671 Forsman, Anders; Folsch, G.; Larsson, M.; Ohman, R. Departments of Psychiatry III, Lillhagan's Hospital, S-42203 Hisings Backa, Sweden **On the metabolism of haloperidol in man.** Current Therapeutic Research. 21(4):606-617, 1977.

A study of the metabolism of haloperidol in man is presented. In the metabolism of haloperidol is man initial cleavage of the molecule at the C/N bond of the central chain is followed by the formation of fluorophenylcarbonic acids in free or conjugated form. Thus, 4-fluorobenzoylpropionic acid and 4-fluorophenylaceturic acid have been isolated from urine and characterized. The formation of glutamine or glucuronic aid derivatives could not be demonstrated. Traces of haloperidol were found to be excreted unmetabolized in the urine. No attempt was made to study the metabolic fate of the piperidine containing residue of the molecule. Degradation of haloperidol does not seem to result in the production of psychoactive metabolites. 4 references. (Author abstract modified)

003672 Frank, P. no address **Comparisons of various clomipramine (Anafranil) dosage regimes.** Journal of International Medical Research (Northampton). 5(Supplement 1):11-15, 1977.

At a symposium held at Rabat, Malta, in November, 1976, four dosage regimes of clomipramine -- 10mg t.d.s.,30mg o.n.,25mg t.d.s. and 75mg o.n. -- were discussed in patients

seen in general practice suffering from depression and information on steady state blood levels of unchanged drug and major metabolite was gathered. However, clinical assessments were also made on a seventeen symptom depression rating scale initially and after 1, 2, and 4 weeks treatment and side-effects were assessed. Seventy patients were admitted to the study; forty nine completed it. All four treatment groups showed significant improvement. The groups were small and no significant differences emerged between them. The best response of 77% improvement on total score after 4 weeks was obtained in the group of patients receiving 25mg t.d.s. The patients on 30mg daily showed a 67% response when this was divided and 65% when given singly. The worst response was obtained in the patients receiving 75mg single dose (50%). Thirteen of the twenty dropouts did so because of side-effects. Ten of these were in high dose groups. However, amongst patients who completed the study there was no difference in the side-effects observed in the four groups. (Journal abstract modified)

003673 Gaillard, Anthony W. K. Institute for Perception TNO, Soesterberg, The Netherlands **Drug effects on EEG frequency spectra as a function of interstimulus interval.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(3):417-420, 1970.

The effects of phentermine HCl, an amphetamine derivative, and hexobarbital sodium, a barbiturate, on the frequency spectra of electroencephalogram (EEG) background activity preceding the stimulus in a serial simple reaction time (RT) task were investigated as a function of interstimulus interval (ISI) in a double-blind study 0f 16 males. The percentage of power in the alpha and theta bands increased with longer ISIs, while the delta activity decreased. The increase in alpha activity with longer ISI conditions was larger after barbiturate, but remained constant after amphetamine treatment. Contrary to expectation, no systematic changes in alpha activity were found during the 3 hr sessions of any of the treatments. It was suggested that the background EEG during the foreperiod of an RT task mainly reflects phasic arousal. The characteristics of the background EEG in the present experimental situation may be quite different from that recorded under "relaxed" no task conditions. 11 references. (Author abstract modified)

003674 Glassman, Alexander H.; Shostak, Michael; Kantor, Shepard J.; Perel, James M. College of Physicians and Surgeons, Columbia University, New York, NY 10032 **Antidepressant plasma levels.** In: Fann, W., Phenomenology and treatment of depression. New York, Spectrum, 1977. 350 p. (p. 265-271).

In a paper presented to a symposium on Phenomenology and Treatment of Depression held at Baylor University in December, 1975, the variable plasma steady state levels observed in patients receiving the same oral dose of a tricyclic antidepressant are discussed. Studies conducted with imipramine and nortriptyline are reviewed. These have shown the marked variability in plasma levels to be primarily the result of individual differences in the rate of drug metabolism. It is now clear also that the large individual variability in plasma steady state levels affects response rate in the cases of imipramine and nortriptyline, and this is thought to apply with amitriptyline and desmethylimipramine as well. 13 references.

003675 Greenblatt, David J.; Joyce, Thomas H.; Comer, Walter H.; Knowles, John A.; Shader, Richard I.; Kyriakopoulos, Adrian A.; MacLaughlin, Dean S. Clinical Pharmacology Unit, Massachusetts General Hospital, Boston, MA 02114 **Clinical pharmacokinetics of lorazepam. II. intramuscular injection.** Clinical Pharmacology and Therapeutics. 21(2):222-230, 1977.

The absorption and disposition of lorazepam were investigated after intramuscular injection of a single 4mg dose to healthy subjects. Lorazepam was rapidly absorbed from the injection site, reaching peak plasma concentrations within 3 hr. The apparent absorption half-life of unchanged lorazepam was 21.2min, the eliminat6on half-life was 13.6hr, the volume of distribution was 0.9liters/kg, and total clearance was 58.2ml/min. The major metabolite of lorazepam, lorazepam glucuronide, rapidly appeared in plasma, reached peak concentrations within 12 hr, and was eliminated approximately in parallel with the parent drug. Within 24 hr, a mean of 47.6% of the dose was recovered in the urine as lorazepam glucuronide and less than 0.5% was recovered as unchanged lorazepam. 45 references. (Author abstract modified)

003676 Hayes, Ronald; Price, Donald D.; Dubner, Ronald. Neurobiology and Anesthesiology Branch, National Insititute of Dental Research, NIH, Bethesda, MD 20014 **Naloxone antagonism as evidence for narcotic mechanisms.** Science. 196(4290):600, 1977.

In a letter in reply to an article by Jean L. Marx on naloxone antagonism of both acupuncture induced and narcotic induced analgesia, the assumption that both analgesias are mediated by the same neural mechanisms is disputed. The existence of at least two physiologically distinct mechanisms capable of modulating responses to painful stimuli are pointed out, and the need for rigorous research strategies to distinguish narcotic from nonnarcotic mechanisms of analgesia are urged. It has long been recognized that naloxone antagonism is necessary but not sufficient to infer a narcotic mechanism of action. 4 references.

003677 Hayes, Sherrard L.; Pablo, Gary; Radomski, Teresa; Palmer, Roger F. Dept. of Pharmacology, University of Miami School of Medicine, PO Box 520875, Biscayne Annex, Miami, FL 33152 **Ethanol and oral diazepam absorption.** New England Journal of Medicine. 296(4):186-189, 1977.

Despite widespread use and abuse of ethanol and diazepam in combination, little is known about the effects of ethanol on diazepam absorption. Diazepam with water and with 30 ml of 50% ethanol was administered to seven normal volunteers. Plasma diazepam levels were significantly higher at 60 minutes, 90 minutes, 120 minutes, and 240 minutes when diazepam was administered with ethanol than with water alone. Since maximum mean plasma diazepam levels after combined ingestion with ethanol were nearly twice as high than after diazepam and water, it is concluded that ethanol enhanced diazepam absorption. 16 references. (Author abstract)

003678 Horrom, Nancy J.; Brown, Clinton C. Biomedical Sciences Division, Maryland Psychiatric Research Center, Baltimore, MD 21228 **Sex differences in drug evaluations.** Journal of Pharmaceutical Sciences. 66(5):739-741, 1977.

To establish sex differences in drug evaluations, a double-blind study was carried out in 20 normal, nonobese subjects (10 male and 10 female) who were administered a battery of seven psychomotor tests as well as affect checklists and physiological measurements on 6 alternate days. Subjects performed the entire battery predrug and at 45, 90 and 135 min postdrug. Fenfluramine, dextroamphetamine, two combined doses of the drugs, and a placebo were given in a double-

blind, repeated measures design. Findings revealed significant sex based differences in initial performance on five of the seven psychomotor tasks and in two physiological measures, with males performing at higher levels than females. Additionally, sex differences in postdrug changes were found in three psychomotor and two physiological measures, with females evidencing greater change scores than males. 15 references. (Author abstract modified)

003679 Jones, R. B.; Luscombe, D. K. Applied Pharmacology Laboratories, Welsh School of Pharmacy, UWIST, Cathays Park, Cardiff, Wales **Plasma level studies with clomipramine (Anafranil).** Journal of International Medical Research (Northampton). 5(Supplement 1):98-107, 1977.

At a symposium held at Rabat, Malta, in November, 1976, plasma level studies were made with clomipramine on 28 patients showing symptoms of depressive illness using four dosage schedules over 28 days. Blood was sampled on admission to the study and at days 7, 14 and 28. Plasma analysis revealed that steady state concentrations of clomipramine and its main metabolite desmethylclomipramine were reached at day 7 of treatment in each of the dosage groups. No apparent relationship between dosage and plasma level of clomipramine was found in this study since there was no significant difference between mean steady state plasma levels in each of the four dosage regimes. In contrast, plasma concentrations of desmethylclomipramine appeared to be directly related to the dose of clomipramine administered. Intersubject variations in plasma levels of the parent compound within each dosage group ranged from three to fourteen fold. 25 references. (Journal abstract modified)

003680 Kalow, W.; Kadar, D.; Inaba, T.; Tang, B. K. Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada **A case of deficiency of N-hydroxylation of amobarbital.** Clinical Pharmacology and Therapeutics. 21(5):530-535, 1977.

A sibship, two female identical twins, in which a genetically controlled deficiency of amobarbital metabolism resulting in a gross deficiency of N-hydroxyamobarbital (N-OH) elimination in urine was found is described. The whole set of sibship data suggests that this deficiency represents a recessive trait controlled by a single pair of allelic autosomal genes which regulate N-OH formation. Several methodical approaches to assess an individual's capacity for N-OH formation are illustrated. There was no evidence of compensatory or concordant regulation of the two hydroxylation reactions. The case of this family illustrates that the functional lack of a biotransformation reaction is almost certain to be overlooked if one measures only the disappearance of a multimetabolized drug and not the appearance of metabolites. 23 references. (Author abstract)

003681 Kavallinis, George P. Northville State Hospital, 41001 W. Seven Mile Road, Northville, MI 48167 **/Lithium -- mechansim of action similar to phenytoin./** Lithium in epilepsy. Clinical Electroencephalography. 8(1):51-56, 1977.

Four case studies are reported of treatment with lithium carbonate of patients having clinical and EEG evidence of convulsive disorder in support of the clinical and EEG impression that lithium carbonate may be beneficial to epileptics or at least is not detrimental in proven convulsive disorders. Lithium treatment for psychosis was associated with improvement of the convulsive component, both clinically and electroencephalographically. One of the cases was unique in that it did not receive conventional anticonvulsant drugs. The serum level of lithium was kept during the course of the illness between 0.7and 1.0mEq/1. It is theorized that lithium has the same biochemical pathway as phenytoin. The possibility that a dose related ionic imbalance between lithium and sodium induces a hyperexcitable membrane would explain conflicting clinical reports about the effects of lithium in epilepsy. 15 references.

003682 Kellermann, Gottfried; Luyten-Kellermann, Mieke. Department of Human Oncology, University of Wisconsin Medical School, Madison, WI 53706 **Phenobarbital-induced drug metabolism in man.** Toxicology and Applied Pharmacology. 39(1):97-104, 1977.

Phenobarbital and antipyrine half-lives were measured in 31 subjects. A high correlation was found for the plasma elimination rates of the two drugs, suggesting the same or a similar route or a common regulatory control of their metabolism. The half-lives of phenobarbital and antipyrine also correlated highly with the aryl hydrocarbon hydroxylase (AHH) inducibilities in mitogen stimulated lymphocytes of the same individuals. In the second part of the study, plasma antipyrine half-lives were measured in 22 subjects after a single oral dose of 18mg/kg, and the AHH inducibilities were determined in their cultured lymphocytes. After 7 days on phenobarbital at aryl hydrocarbon hydroxylase inducibility adjusted doses ranging between 1.0and 2.0mg/kg daily, the antipyrine half-lives were measured again and the percentage of decrease between the initial and second antipyrine half-lives was determined. Shortening of the plasma half-lives occurred in all subjects to various degrees, ranging between 13.3and 30.6%. However, under experimental conditions in which the dose of phenobarbital was adjusted to the individual rates of metabolism of the inducing agent, no relationship could be found between the initial antipyrine half-life and the percentage of shortening of its plasma half-life, such as had been reported by several authors. 25 references. (Author abstract)

003683 Klotz, U.; Antonin, K. H.; Brugel, H.; Bieck, P. R. Margarete Fischer-Bosch-Institut fur Klinische Pharmakologie, Auerbackstr., 112, D-7000 Stuttgart 50, Germany **Disposition of diazepam and its major metabolite desmethyldiazepam in patients with liver disease.** Clinical Pharmacology and Therapeutics. 21(4):430-436, 1977.

Elimination of diazepam in 11 patients with liver disease was compared after single and subchronic dosage, and the pharmacokinetics of the major metabolite of diazepam, desmethyldiazepam, are compared with its parent compound. After a single dose of diazepam, liver diseased patients had a significantly longer half-life than healthy control Ss, but this difference did not hold up under subchronic treatment for 7 days. After intravenous injection of desmethyldiazepam, plasma levels declined in the same biexponential manner as after diazepam. Desmethyldiazepam was eliminated much slower than diazepam. The accumulation of desmethyldiazepam after multiple dosage is explained by the fact that it is formed faster from diazepam than it is eliminated. Results indicate that at least two steps are impaired in diazepam metabolism in patients with liver disease. 12 references.

003684 Langer, Gerhard; Sachar, Edward J.; Gruen, Peter H.; Halpern, Frieda S. Dept. of Psychiatry, College of Physicians & Surgeons, Columbia Univ., 722 W. 168th St., New York, NY 10032 **Human prolactin responses to neuroleptic drugs correlate with antischizophrenic potency.** Nature (London). 266(5603):639-640, 1977.

To determine if a correlation exists between prolactin releasing effects and antischizophrenic potencies of neuroleptics, 12 healthy male students were administered haloperidol, chlor-

promazine, prochlorperazine, trifluoperazine, perphenazine, fluphenazine, and thiothixene intramuscularly and prolactin assays were carried out on blood samples. Results indicated that these antischizophrenic drugs showed a very high correlation between their prolactin releasing and antischizophrenic potencies. It is hypothesized that mechanisms mediating these two different drug effects both serve to block dopaminergic transmission. 14 references.

003685 Luscombe, D. K. Applied Pharmacology Section, Welsh School of Pharmacy, UWIST, Cathays Park, Cardiff, Wales **Factors influencing plasma drug concentrations.** Journal of International Medical Research (Northampton). 5(Supplement 1):82-97, 1977.

At a symposium held at Rabat, Malta, in November, 1976, factors influencing plasma drug concentrations and the influences upon the safety and efficacy of treatment are discussed. A number of factors may influence these levels. Levels may be affected by age, bodyweight and size, genetical factors, abnormalities of water and electrolyte balance and complications associated with pathological conditions such as renal and hepatic impairment. Likewise, plasma levels will depend on dosage, time, and route of drug administration, the bioavailability of the drug and time of blood sampling. In addition, absorption, distribution, metabolism, excretion, and concurrent drug administration may profoundly affect plasma drug concentrations. 76 references. (Journal abstract modified)

003686 Marini, James L. Department of Psychiatry, Yale University School of Medicine and Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06508 **On the significance of the erythrocyte lithium to plasma lithium ratio.** British Journal of Psychiatry. 130:139-143, 1977.

The mechanism of lithium distribution across the ratio of erythrocyte (RBC) membrane is discussed, and the consistency of studies reporting correlations of lithium concentration (Le) to plasma lithium concentration (Lp) with clinical status is examined. It is suggested that unless the factors governing accumulation of lithium ion by RBC are clarified, the relevance of Le/Lp determinations to an understanding of affective illness must be questioned. Examination of the literature on Le/Lp and erythrocyte physiology suggests that Le/Lp is determined by pharmacokinetic parameters unrelated or indirectly related to psychiatric illness, and because studies reporting correlations between Le/Lp and psychiatric status do not agree with each other, measurement of Le/Lp is unlikely to illuminate either the pathophysiology of affective disorders or the mode of action of lithium. It is concluded that critical tests of the proposed kinetic control of Le/Lp in clinical studies would be more appropriate than attempts to correlate the ratio with psychiatric diagnosis. 17 references. (Author abstract modified)

003687 Mayer, David J.; Price, Donald D.; Rafii, Amir. Department of Physiology, Medical College of Virginia, Richmond, VA 23298 **Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone.** Brain Research (Amsterdam). 121(2):368-372, 1977.

The possibility that acupuncture analgesia involves the release of an endogenous substance with narcotic analgesic activity was investigated in humans. Acupuncture increased thresholds to pain produced by electrical stimulation of a tooth by about 27%. Intravenous injections of naloxone in doses having no effect on baseline pain threshold reduced pain thresholds in acupuncture treated subjects to approximately those occurring in a control group. It is suggested that acupuncture in some way results in the release of an endogenous substance with narcotic analgesic activity and that this release occurs within the central nervous system rather than at the acupuncture site. 30 references.

003688 McGinity, James W.; Lach, John L. College of Pharmacy, University of Texas at Austin, Austin, TX 78712 **Sustained-release applications of montmorillonite interaction with amphetamine sulfate.** Journal of Pharmaceutical Sciences. 66(1):63-66, 1977.

The possibility that a sustained release dosage form could be developed by complexing amphetamine with montmorillonite was investigated. Urinary recovery studies showed that montmorillonite affected the initial therapeutic levels of amphetamine sulfate. The combination of a 1:20 amphetamine montmorillonite complex with pure drug in a 1:1 ratio (based on amphetamine content) resulted in recovery profiles resembling those obtained from prolonged release dosage forms. The 1:20 complex, pure drug and combination formulations showed comparable bioavailability after 48 hr. It is suggested that the drug/excipient interaction between cationic drugs and montmorillonite clay might be employed successfully to prolong the action of such medicinals. 11 references. (Author abstract modified)

003689 Meltzer, Herbert Y.; Piyakalmala, Songkait; Schyve, Paul; Fang, Victor S. Department of Psychiatry, University of Chicago Pritzker School of Medicine, 950 E. 59th St., Chicago, IL 60637 **Lack of effect of tricyclic antidepressants on serum prolactin levels.** Psychopharmacology (Berlin). 51(2):185-187, 1977.

An attempt was made to replicate the findings of Turkington that the tricyclic antidepressants imipramine and amitriptyline markedly increase plasma prolactin levels in humans. No increases in plasma prolactin levels were found after acute or chronic treatment with usual clinical doses of either drug to 10 depressed hospitalized patients. It is concluded that blockade of serotonin reuptake does not affect basal prolactin levels in man and that if these drugs did block serotonin uptake in the human hypothalamus, then the serotonergic stimulation of prolactin secretion is not a significant factor in determining basal prolactin secretion. 23 references. (Author abstract modified)

003690 Miest, Peter-Chr.; Schwarz, E.; Kielholz, P.; Goldberg, L.; Hobi, V.; Ladewig, D.; Reggiani, G.; Richter, R. Psychiatrische Universitatsklinik Basel, Wilhelm-Klein-Strasse 27, CH-4025 Basel, Switzerland **The heart rate response as an indicator of changes in activation induced by alcohol.** International Journal of Clinical Pharmacology and Biopharmacy (Munchen). 15(1):40-47, 1977.

The effects of alcohol on the acoustic evoked heartrate response (HRR) were studied among 12 healthy male volunteers. Subjects also assessed their moods, estimated degree of intoxication, and degree of fright in response to the first audition stimulus. Significant depressant effects were reflected in decreases in the HRR acceleration, vitality, vigilance and self-estimated startle reaction. Stimulating effects were also observed, reflected by increases of the mean heartrate and the second HRR deceleration. It is concluded that different alcohol induced states of activation represent different patterns of inhibitory processes and facilatory processes, each manifesting itself in different parameters. Three major components of alcohol action are suggested: 1) an inhibition release with immediate onset, 2) a slower processing inhibition, and 3) attention focusing as a compensatory response to inhibition. 22 references. (Author abstract modified)

003691 Mullen, Ann; Wilson, C. W. M.; Wilson, B. P. M. Department of Pharmacology, Trinity College, Dublin, Ireland **Dreaming, fenfluramine, and vitamin C.** British Medical Journal (London). No. 6053:70-72, 1977.

The effect of increasing doses of fenfluramine on dream patterns was studied in 20 patients receiving a reducing diet with or without a controlled dietary intake of vitamin C daily. The dream pattern was unchanged in six patients and dreams disappeared in another who normally dreamed often. In 13 patients dreams increased in frequency and intensity, and in five the dreams assumed frightening proportions. There was a significant straightline relation between response and the size of the dose. When placebo tablets were given to four patients their dreams disappeared or assumed their pretreatment normal pattern. Absence of vitamin C from the diet did not significantly affect the dream pattern. That fenfluramine has dose related cerebral effects should be remembered in patients with a history of mental illness. 28 references. (Journal abstract)

003692 Murphy, D. L.,; Brand, E; Goldman, T.; Baker, M; Wright, C.; van Kammen, D.; Gordon, E. NIH Clinical Center 10-3S220, Bethesda, MD 20014 **Platelet and plasma amine oxidase inhibition and urinary amine excretion changes during phenelzine treatment.** Journal of Nervous and Mental Disease. 164(2):129-134, 1977.

Platelet and plasma amine oxidase inhibition and urinary amine excretion changes occuring during phenelzine treatment was investigated in 15 patients with primary depressive disorders. The treatment of depressed patients with the monoamine oxidase (MAO)inhibiting antidepressant, phenelzine, was found to be accompanied by an 82% reduction in platelet MAO activity and a 91% reduction in plasma amine oxidase activity. Maximum reductions in enzyme activity occurred after seven to fourteen days of treatment; recovery of enzyme activity posttreatment required an average of fourteen days for the platelet MAO and greater than six weeks for the plasma enzyme. Marked elevations in urinary tryptamine excretion occurred in conjunction with MAO inhibition during phenelzine treatment, but the magnitude of urinary tryptamine change in individual patients was not closely correlated with the magnitude of enzyme activity reduction. Changes in platelet serotonin content and in urinary catecholamine metabolites also occurred in response to phenelzine treatment. 35 references. (Author abstract modified)

003693 Nikitopoulou, Georgia; Thorner, Michael; Crammer, John; Lader, Malcolm. Institute of Psychiatry, De Crespigny Park, London S.E. 5, England **Prolactin and psychophysiologic measures after single doses of thioridazine.** Clinical Pharmacology and Therapeutics. 21(4):422-429, 1977.

Prolactin and various psychophysiological measures were assessed after single doses of thioridazine to clarify the nature of individual responses to psychotropics. Six normal men ingested thioridazine, high and low doses, and placebo on three occasions. Their plasma and urinary thioridazine and mesoridazine plus sulforidazine were measured over 5 hr, together with their plasma prolactin, and a battery of psychophysiologic variables. Drowsiness and EEG changes correlated highly with rise in prolactin, but not with drug plasma concentrations. Finger tremor increased, and some psychologic tests were impaired by thioridazine; other psychologic tests, the auditory evoked response, and palmar skin conductance were unaffected and showed no relationship to drug or prolactin levels. This suggests that plasma prolactin may be a useful indicator of some aspects of the individual's response to a psychotropic drug, and possibly a better guide to the selection of a suitable drug and its appropriate dose in clinical practice than the measurement of plasma concentrations of the drug itself. 11 references. (Author abstract)

003694 Olsen, George D.; Wendel, Herbert A.; Livermore, James D.; Leger, Regina M.; Lynn, Robert K.; Gerber, Nicholas. Department of Pharmacology, School of Medicine, University of Oregon Health Sciences Center, Portland, OR 97201 **Clinical effects and pharmacokinetics of racemic methadone and its optical isomers.** Clinical Pharmacology and Therapeutics. 21(2):147-157, 1977.

The respiratory effects, pupillary effects and antidiuretic effects of oral levomethadone, dextromethadone and racemic methadone were studied in healthy male volunteers. The mean half-life of drug in blood was 22 hr for racemic methadone, 24 hr for levomethadone and 25 hr for dextromethadone. Both 7.5mg of levomethadone and 5mg of racemic methadone produced intense and sustained respiratory depression and miosis, but dextromethadone produced slight respiratory depression only in doses of 50mg or above. The changes induced by levomethadone were of longer duration than those of racemic methadone, lasting more than 72 hr in some subjects. Whole blood drug concentration correlated well with respiratory depression and miosis for levomethadone and racemic methadone. The antidiuretic effect of 15 mg of racemic methadone persisted for as long as measurements were taken (up to 12 hr). It is suggested that racemic methadone, if administered frequently for pain, may have cumulative effects on respiratory control and diuresis. 27 references. (Author abstract modified)

003695 Overo, K. Fredricson; Gram, L. F.; Hansen, V. Research Laboratories, H. Lundbeck and Co. A/S, Ottiliavej 7-9, DK-2500 Valby, Denmark **Interaction of perphenazine with the kinetics of nortriptyline.** Acta Pharmacologica et Toxicologica (Kobenhavn). 40(1):97-105, 1977.

The pharmacokinetics of nortriptyline before and during treatment with perphenazine were investigated in four mildly psychotic patients by administering nortriptyline hydrochloride as an intravenous infusion and evaluating the resulting plasma concentration data according to a two compartment open model. In all patients, an increased biological half-life as well as a decreased systemic clearance and rate of metabolism were found during perphenazine administration, thus confirming the inhibitory effect of perphenazine on the metabolism of nortriptyline found in earlier studies. Although some effects on nortriptyline distribution were also found, the model parameters did not provide much further information about the interaction. Although the most pronounced changes occurred in the patient receiving the highest dose of perphenazine, the dose/effect relationship remains obscure. 25 references. (Author abstract modified)

003696 Padfield, P. L.; Park, S. J.; Morton, J. J.; Braidwood, A. E. Medical Research Council, Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT, Scotland **Plasma levels of antidiuretic hormone in patients receiving prolonged lithium therapy.** British Journal of Psychiatry. 130:144-147, 1977.

A high incidence of increased thirst and frequency of micturition (60 to 70 per cent) was noted on direct questioning. Symptoms arose at varying times after the start of lithium therapy; in no patient did symptoms antedate the use of the drug. Plasma levels of antidiuretic hormone were found, on average, to be higher than in normal control subjects for a given level of plasma osmolality, although the scatter of results was wide. It is suggested that elevation of antidiuretic

hormone occurs as a compensatory mechanism for the polyuria which is a common feature of long- term lithium treatment. The more florid form of nephrogenic diabetes insipidus occasionally seen in lithium takers seems likely to be due to a different mechanism from the more common mild polyuria. Plasma levels of antidiuretic hormone were studied in 18 patients receiving long-term prophylactic lithium treatment for manic-depressive psychosis. 22 references. (Author abstract modified)

003697 Painter, Michael J.; Pippinger, Charles; Carter, Gertrude; Pitlick, William. no address **Metabolism of phenobarbital and phenytoin by neonates with seizures.** Neurology. 27(4):370, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, the metabolism of phenobarbital (PB) and phenytoin (PT) was studied in 77 neonates with seizures utilizing the EMIT system. Following intravenous (iv) loading doses of 15 to 20mg/kg, PB and PT levels of 19.4and 14.9L/kg were achieved, respectively; the volumes of distribution of PB and PT were 0.97 and 1.19, respectively, and were not influenced by gestational age. Oral, iv, or intramuscular maintenance PB at 5mg/kg/day, following iv loading resulted in levels of 28mg/L on days 1 to 4. There was a tendency of accumulation on days 5 to 10, with levels of 33.5mg/L. Levels decreased to 30.3on days 10 to 20 and 17.4after day 20. The change in PB metabolism also was reflected in a decreasing half-life of PB with increasing time of exposure to the drug. Therapeutic levels of PT were maintained with iv medication, but in none of 13 neonates could therapeutic levels be achieved by the oral route.

003698 Perez, Guido O.; Oster, James R.; Magrinat, Gaston; Vaamonde, Carlos A. Veterans Administration Hospital, 1201 Northwest 16th St., Miami, FL 33125 **Effect of long-term lithium administration on renal phosphorus handling.** Clinical Pharmacology and Therapeutics. 21(4):449-452, 1977.

Renal phosphorus handling was evaluated in 12 lithium carbonate treated psychiatric patients. Serum phosphorus was normal and serum lithium values were within the therapeutic range in all subjects. Serum calcium concentrations measured in six of the patients were found to be within the normal range; in the same patients serum parathyroid hormone levels were normal in four and slightly elevated in two. Phosphorus clearance and tubular reabsorption of phosphorus during oral sodium bicarbonate loading were not significantly different from those in 10 healthy control subjects. In a subgroup of five patients and five control subjects, phosphorus excretion did not increase after bicarbonate loading. In these subjects, phosphorus excretion rates after bicarbonate loading were not different. Although experimental studies suggest that lithium inhibits renal cortical adenylate cyclase stimulation by parathyroid hormone, this data did not indicate any striking effect of long-term lithium administration on serum calcium and serum phosphorus or on renal phosphorus handling. 7 references. (Author abstract)

003699 Persson, G. Department of Psychiatry, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden **Comparison of plasma lithium levels and their interindividual variations with coated lithium carbonate tablets and a medium-slow-release lithium sulphate preparation (Lithionit Duretter).** Acta Psychiatrica Scandinavica (Stockholm). 55(2):147-152, 1977.

In a cross-over study in 10 subjects, rapidly dissolving coated lithium carbonate tablets and medium slow release lithium sulphate tablets were compared. Both preparations were administered twice a day. They gave similar postabsorptive concentrations of lithium in plasma and similar standard deviations of these concentrations. The medium slow release tablets gave smaller increases of lithium in plasma, and postponed the absorption peaks. They also gave less interindividual variation of lithium in plasma during the first few hours after administration. 9 references. (Journal abstract)

003700 Poust, R. I.; Mallinger, A. G.; Mallinger, J.; Himmelhoch, J. M.; Neil, J. F.; Hanin, I. Department of Pharmaceutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261 **Absolute availability of lithium.** Journal of Pharmaceutical Sciences. 66(4):609-610, 1977.

A study using an indirect method for calculating absolute bioavailability based on perturbation of renal clearance to determine absorption of lithium carbonate from a commercially available preparation is reported in a letter to the editor. Plasma concentrations of lithium were determined periodically for 30 hr after ingestion of a 300mg capsule of lithium carbonate before and after administration of chlorothiazide to four healthy subjects to determine the effects of chlorothiazide on the renal clearance of lithium. The change in renal clearance resulting from the changes in experimental conditions, the dose administered, and the areas under the plasma concentration/time curves for the two experimental conditions were used to calculate the fraction of dose absorbed. It was found that the brand of lithium carbonate tested is completely absorbed. 7 references.

003701 Reid, J. L.; Wing, L. M. H.; Mathias, C. J.; Frankel, H. L.; Neill, E. Department of Clinical Pharmacology, Royal Postgraduate Medical School, Du Cane Road, London W.12. OHS, England **The central hypotensive effect of clonidine: studies in tetraplegic subjects.** Clinical Pharmacology and Therapeutics. 21(4):375-381, 1977.

The effects of a single oral dose of clonidine on five healthy, normotensive control Ss were compared to those effects on six tetraplegic Ss with physiologically complete chronic cervical spinal cord transection above the level of the sympathetic outflow. Although blood pressure fell in the control Ss, it did not in the tetraplegic Ss. Peak plasma concentrations of clonidine, measured by mass fragmentograph, and elimination of the drug from plasma were similar in tetraplegic and control subjects and there was no difference in the incidence of the principal side-effects of clonidine -- sedation and dry mouth. Although the number of subjects studied is small, the absence of a fall in blood pressure after clonidine in the tetraplegic subjects suggests that the hypotensive action of clonidine in man is dependent on intact descending bulbospinal pathways and is mediated by withdrawal of sympathetic tone and provides direct evidence that some antihypertensive drugs may lower blood pressure in man by a direct action on the brain. 32 references. (Author abstract)

003702 Roots, I.; Ick, A.-M.; Holbe, R.; Leonhardt, H.; Palme, G. Institut fur Klinische Pharmakologie der Freien Universitat Berlin, Klinikum Steglitz, D-1000 Berlin 45, Hindenbergdamm 30, Germany **Influence of phenobarbital on liver function and drug metabolism in patients with alcoholic liver cirrhosis.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 297(Supplement 2):R60, 1977.

A study of the influence of phenobarbital on liver function and drug metabolism in patients with alcoholic liver cirrhosis is reported in a paper given at the 18th spring meeting of the Deutsche Paramakologische Gesellschaft, held in Mainz, Germany in March 1977. Data obtained from 21 patients indicated

that liver function in general was not affected by phenobarbital. In contrast, urinary glucaric acid excretion was substantially increased. In spite of highly pathological values of conventional liver function tests, glucaric acid and 6-beta-hydroxy-cortisol excretion were normal in control patients. It is suggested that although the latter parameters permit the demonstration of an increased capacity for drug metabolism such as were found with phenobarbital administration, they are not suitable for measuring a reduced capacity for drug metabolism. (Author abstract modified)

003703 Schachter, Stanley; Silverstein, Brett; Perlick, Deborah. Department of Psychology, Columbia University, New York, NY 10027 **Studies of the interaction of psychological and pharmacological determinants of smoking: 5. psychological and pharmacological explanations of smoking under stress.** Journal of Experimental Psychology: General. 106:(1):31-40, 1977.

In one of a series of five studies of the interaction of psychological and pharmacological determinants of smoking, the psychological state of stress is pitted against urinary pH to learn if pH changes are a necessary mediator of the stress smoking relation. It was discovered that when stress and pH of the urine were independently manipulated, smoking tracked pH, not stress, and that when urinary pH was experimentally maintained at alkaline levels, psychological stress had no effect on smoking. This set of facts is viewed as providing support for the hypothesis that heavy smokers smoke for nicotine, and more specifically, as indicating that the urinary pH mechanism is the crucial biochemical mediator of the stress smoking relation. 13 references.

003704 Sedvall, G.; Alfredsson, G.; Bjerkenstedt, L.; Eneroth, P.; Fyro, B.; Harnryd, C.; Wode-Helgodt, B. Departments of Pharmacology and Psychiatry, Karolinska Institutet, S-10401 Stockholm, Sweden **Central biochemical correlates to antipsychotic drug action in man.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 41-54).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December, 1975, studies dealing with correlations between pharmacokinetic factors and biochemical pharmacodynamic factors and therapeutic efficacy of antipsychotic drugs were reported. It has been found that: 1) there is a correlation between cerebrospinal fluid (CSF) levels of chlorpromazine (CPZ) and the degree of improvement in psychotic patients; 2) the levels of CPZ in the CSF do not always correlate with the dosage given; and 3) optimal antipsychotic effects occur with CSF levels of 1ng/ml or more of CPZ. Studies investigating the correlation between therapeutic efficacy and biochemical parameters such as the effects of various neuroleptics on CSF concentrations of homovanillic acid (HVA), methoxyphenylethylene glycol (MOPEG), and 5-hydroxyindoleacetic acid, (5-HIAA) (reflecting alterations in cerebral dopamine (DA), noradrenalin (NA), and serotonin (5-hydroxytryptamine), respectively) and the effects of CPZ on CSF prolactin levels were reviewed. Data from these studies revealed that: 1) some neuroleptics (i.e. thiothixene) elevate CSF HVA levels and have no effect on MOPEG or 5-HIAA levels; 2) other neuroleptics (i.e. chlorpromazine) elevate CSF levels of HVA while reducing MOPEG and 5-HIAA levels; 3) for three types of chemically different antipsychotic drugs, the HVA/MOPEG ratio is increased during treatment, and greater changes in the HVA/MOPEG ratio are correlated with greater improvement; and 4) a positive correlation also exists between elevation of the prolactin level in CSF during CPZ therapy and the change in clinical condition, with this effect appearing to be more significant in men than in women. It is suggested that the demonstration of relationships between clinical efficacy and pharmacokinetic and biochemical parameters may be of value for the selection of optimal drug dosage in psychotic patients as well as for understanding the pathophysiological mechanisms involved in psychotic states. 7 references.

003705 Shader, Richard I.; Greenblatt, David J.; Harmatz, Jerold S.; Franke, Kate; Koch-Weser, Jan. Massachusetts Mental Health Center, 74 Fernwood Road, Boston, MA 02115 **Absorption and disposition of chlordiazepoxide in young and elderly male volunteers. (Unpublished paper).** Rockville, MD, NIMH, 1977. 21 p.

The pharmacokinetics of oral chlordiazepoxide (CDX) were studied in 28 young (mean age: 25 years) and 8 elderly (mean age: 69 years) male volunteers, all of whom were in good health and administered 25mg of chlordiazepoxide (CDX) hydrochloride with water in the fasting state. Multiple venous blood samples drawn during 25 hours after the dose were assayed for concentrations of CDX and its major pharmacologically active metabolite, desmethylchlordiazepoxide (DMCDX). Peak CDX blood levels in the elderly subjects were lower and reached later after the dose than in the young volunteers, suggesting a slower rate of absorption in the elderly. The mean elimination half-life of CDX in the elderly (18.2hours) was significantly longer than in the young subjects (10.1hours), and CDX clearance in the elderly (26.6ml/min) was significantly less than in the young (46.3ml/min). Appearance in the blood of DMCDX also was significantly reduced in the elderly. The findings were not influenced by smoking habits or by concurrent use of other drugs. Because of its decreased clearance in elderly individuals, accumulation of CDX during chronic therapy may be greater in elderly than in young patients. The clinical significance of this is not established, since generation of the pharmacologically active metabolite DMCDX is also reduced. 28 references. (Author abstract)

003706 Shimizu, Muneo; Smith, Donald F. Department of Neuropsychiatry, Tokyo Medical College Hospital, 6-7-1 Nishishinjuku, Tokyo, Japan **Salivary and urinary lithium clearance while recumbent and upright.** Clinical Pharmacology and Therapeutics. 21(2): 212-215, 1977.

The excretion of lithium in urine and saliva was studied in healthy males while recumbent and while upright. Urinary lithium clearance decreased when posture was changed from recumbent to upright, but salivary lithium clearance was not affected by the abrupt change in posture. A correlation between lithium clearance in urine and saliva was observed while recumbent but not while upright. The findings are related to the extrapolation of saliva lithium excretion data to urinary lithium clearance. 10 references. (Author abstract modified)

003707 Silverstein, Brett; Kozlowski, Lynn T.; Schachter, Stanley. Department of Psychology, Princeton University, Princeton, NJ 08540 **3. Social life, cigarette smoking, and urinary pH.** Journal of Experimental Psychology: General. 106(1):20-23, 1977.

In one of a series of five studies of the interaction of psychological and pharmacological determinants of smoking, the effect of party going on smoking and the effect of party going on urinary pH were studied, in an effort to learn if the reported effects of party going on cigarette smoking may be

explainable by purely pharmacological considerations, i.e, the effects of urinary pH on the rate of excretion of unmetabolized urine. In one study it was indicated that party going increases smoking and decreases urinary pH. In a second study, party goers had a reduced pH, while nonparty goers pH remained unchanged during similar hours. It was concluded that increased smoking and decreased pH were affected by party going. 4 references.

003708 Sitaram, Natraj; Buchsbaum, Monte S.; Gillin, J. Christian. Adult Pschiatry Branch, Division of Clinical and Behavioral Research, NIH, Bethesda, MD 20014 **Physostigmine analgesia and somatosensory evoked responses in man.** European Journal of Pharmacology (Amsterdam). 42(3):285-290, 1977.

Physostigmine analgesia and somatosensory evoked responses were studied in a randomized double-blind trial with 14 normal volunteers. The subjects were pretreated with methscopolamine. Pain ratings and average evoked responses were obtained to brief electrical stimuli administered to the forearm. Pain response criterion was significantly higher on physostigmine than on placebo. Average evoked response component P100 was significantly smaller on physostigmine than placebo, especially for higher intensity stimuli. These results are consistent with central cholinergic modulation of pain and arousal systems in man. 25 references. (Author abstract modified)

003709 Siwers, Bo; Ringberger, Vivi-Ann; Tuck, J. Richard; Sjoqvist, Folke. Department of Clinical Pharmacology, Huddinge Hospital, S-141-86 Huddinge, Sweden **Initial clinical trial based on biochemical methodology of zimelidine (a serotonin uptake inhibitor) in depressed patients.** Clinical Pharmacology and Therapeutics. 21(2):194-200, 1977.

Zimelidine, 1 bicyclic compound having a pronounced inhibitory effect on neuronal 5-hydroxtryptamine (5-HT) uptake in animals, was administered to six depressed patients and its biochemical effects monitored. Plasma from the patients markedly inhibited 5-HT uptake compared to norepinephrine (NE) uptake. The inhibitory effect on 5-HT uptake and the plasma concentration of the desmethylated metabolite correlated significantly. The 5-hydroxyindoleacetic acid (5-HIAA) levels in cerebrospinal fluid decreased markedly in four patients while the indoleacetic acid (IAA) levels increased. The levels of 4-hydroxy-3-methoxyphenylglycol (HMPG) also decreased significantly, but less so than the 5-HIAA levels. The effects on homovanillic acid (HVA) were inconsistent. It is suggested that zimelidine is a selective inhibitor of 5-HT uptake in central monoamine neurons and is an interesting pharmacologic tool for future central nervous system research. 20 references. (Author abstract modified)

003710 Straumanis, John J., Jr.; Shagass, Charles. Department of Psychiatry, Temple University, Philadelphia, PA 19122 **Effects of lithium, triiodothyronine, and propranolol on human somatosensory-evoked potentials.** Psychopharmacology Bulletin. 13(2):58-59, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, the effects of lithium (Li), triiodothyronine, (T3), and propranolol (PRO) on human somatosensory evoked potentials were studied. Somatosensory evoked response (SER) characteristics were investigated by stimulating the right median nerve at the wrist and recording SERs from a bipolar derivation over the left hemisphere. Li was given to 5 male and 5 female patients and 4 male volunteers; T3 and PRO were given only to male volunteers. Li increased SER amplitude in female patients, but not in male patients or volunteers. T3 increased SER amplitude, but did not alter SER recovery. Addition of PRO eliminated the SER amplitude increase due to T3, although PRO alone had no significant effects on SER amplitude or recovery. Li altered recovery. By digitally filtering the SER into 2 frequency bands, the Li effect was shown to be limited to the fast (32 to 500Hz) frequency range, but the T3 effect was also found below 32Hz. The PRO reversal of SER changes produced by T3 indicates a central action of the beta-adrenergic blocking agent. An investigation of the somatosensory evoked response effects of lithium in healthy females is required to establish whether the Li effect reflects a sex difference or an illness related process. 6 references.

003711 Sulkowski, A.; Vachon, L.; Rich, E. S., Jr. Psychatirc Research Laboratory, Boston University School of Medicine, 720 Harrison Avenue, Boston, MA 02118 **Propranolol effects on acute marihuana intoxication in man.** Psychopharmacology (Berlin). 52(1):47-53, 1977.

Six healthy experienced marihuana smokers received propranolol and marihuana alone and in combination to investigate the effects of the beta-adrenergic blocking agent on marihuana induced changes in perception and behavior. Propranolol reduced resting heartrate (HR) and blood pressure (BP) but had no effect on performance of tasks designed to test psychomotor speed attention, memory and learning. Marihuana administered in smoke induced the typical subjective state ("high") with marked increased in HR, BP, and conjunctival injection; it impaired performance on a learning test without significantly affecting attention. Pretreatment with propranolol effectively blocked the cardiovascular effects of marihuana; it prevented the learning impairment and, to a lesser degree, the characteristic subjective experience. 33 references. (Author abstract modified)

003712 Sullivan, John L.; Dackis, Charles; Stanfield, Charles. Veterans Administration Hospital, 508 Fulton St., Durham, NC 27705 **In vivo inhibition of platelet MAO activity by tricyclic antidepressants.** American Journal of Psychiatry. 134(2):188-190, 1977.

Platelet MAO activity decreased by 40% in a group of 11 male patients with primary depression after 3 weeks of treatment with either amitriptyline or imipramine. Although the relationship between this pharmacological effect and the clinical action of tricyclic antidepressants remains unclear, the MAO correlates significantly with normalization of sleep patterns in the same group of patients, but not with changes in motor activity. Inhibition of MAO is seen as playing a role in the clinical action of tricyclic antidepressant drugs. 16 references. (Author abstract modified)

003713 Sun, Sy-Rong; Chun, A. H. C. Pharmaceutical Products Division, Abbott Laboratories, North Chicago, IL 60064 **Determination of pentobarbital in serum by electron-capture GLC.** Journal of Pharmaceutical Sciences. 66(4):477-480, 1977.

A new GLC method for the determination of pentobarbital in serum which is sensitive to 0.2ng/injection and uses electron capture detection of the 1,3-bis(pentafluorobenzyl) derivative of pentobarbital is described. The procedure was successfully applied to measurement of serum pentobarbital levels in humans. After a single oral dose of 100mg of pentobarbital sodium to normal subjects, peak levels of drug ranged from 1.2microgram/ml to 3.1microgram/ml and were observed 0.5hr to 2 hr after administration. Substantial quantities of drug were detected 48 hr after administration. 12 references.

003714 Temple, D. J.; Oelschlager, H. Institut fur Pharmazeutische Chemie der Universitat Frankfurt, Georg-Voight-Str. 14, 6 Frankfurt am Main, Germany **Problems on the forensic detection of dextromoramide or its metabolites.** 7(1/2):102, 1977. Xenobiotica (London).

Problems on the detection of dextromoramide, a synthetic narcotic analgesic similar in structure to methadone, and/or its metabolites are discussed in a paper presented at a symposium titled "Drug Metabolism -- from Microbe to Man" held at Guildford, England in April 1976. The fate of dextromoramide was studied in three animal species and in two human volunteers using thin layer chromatography and gas layer chromatography. No unchanged drug was found in any urinary, fecal, or biliary samples, indicating that the drug is rapidly and completely metabolized. For forensic detection, it is suggested that a metabolite found in human and rat urine may prove satisfactory for proving that the drug has been administered. 4 references. (Author abstract modified)

003715 Tseng, Liang-Fu; Loh, Horace H. Department of Psychiatry, University of California, San Francisco, CA 94143 **Effects of methoxyamphetamines on the uptake and release of (3H)5-hydroxytryptamine by human blood platelets.** Biochemical Pharmacology (Oxford). 26(7):647-649, 1977.

The effects of paramethoxyamphetamine (4-MA) and other methoxylated amphetamines on the uptake and release of radiolabeled serotonin (5-hydroxytryptamine, 5-HT) by human blood platelets were studied in order to determine possible correlations between psychotomimetic potencies and the effects on 5-HT uptake and release. Of the monomethoxyamphetamines, 4-MA was most active in increasing the release and blocking the uptake of 5-HT. Dimethoxyamphetamines were less active than monomethoxyamphetamines but more active than trimethoxyamphetamines. It was also determined that paramethoxylation of amphetamine increased, and ortho methoxylation of amphetamine decreased, the effects of the analogues on 5-HT uptake and release. An impressive correlation between the psychotomimetic potencies and the effects on uptake and release of 5-HT was found for the monomethoxyamphetamines but not for the polymethoxyamphetamines. Possible alternative mechanisms for the reported hallucinogenic effects of some polymethoxyamphetamines are discussed. 17 references.

003716 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Neuroleptics and CA-ergic transmission in the brain: clinical studies.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 199-202).

Studies of the effects of neuroleptic drugs on human catecholaminergic transmission in the brain as determined by measuring their effects on monoamine (MA) metabolite concentrations in the cerebrospinal fluid (CSF) are reviewed. Neuroleptics of the receptor blocking type increase both the baseline homovanillic acid (HVA) concentration and the post-probenecid HVA accumulation in human CSF, suggesting that they increase the central dopamine (DA) turnover. As it is in animal experiments, this effect is probably secondary to inhibition of transmission in the dopaminergic system. This may be concluded from the observation that neuroleptics increase serum prolactin concentration, an effect indicative of reduced dopaminergic activity in the tuberoinfundibular system. Oxypertine has no demonstrable effect on human central serotonin or DA metabolism, but increases the 3-methoxy-4-hydroxyphenylglycol concentration in the CSF. This finding is consistent with depletion of central noradrenalin stores. These findings correlate well with those obtained in animal experiments, and support the idea that neuroleptics block catecholaminergic transmission in the human brain.

003717 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Verification of the MA hypothesis with the aid of drugs and other methods of antidepressant therapy: direct influencing of the transmission process.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 107-121).

Possible correlations between the therapeutic effects of various drugs in humans and their biological effects as determined by measurement of their effects on monoamine (MA) metabolite concentrations in urine or cerebrospinal fluid (CSF) in humans or by measurement of their direct effects on MA concentrations in animal CNS are discussed in terms of the MA hypothesis. This hypothesis is a combination of the serotonin (5-hydroxytryptamine, 5-HT) hypothesis and the catecholamine (CA) hypothesis which proposes that disturbances in central CA and/or 5-HT metabolism resulting in an absolute or relative deficiency in these substances is involved in the pathogenesis of depressive and manic syndromes. Studies comparing the therapeutic effects of tricyclic antidepressants having a selective effect on 5-HT or noradrenalin (NA) uptake with their effects on urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG) and CSF levels of 5-hydroxyindoleacetic acid (5-HIAA) indicate that disorders of central MA metabolism are involved in the pathogenesis of endogenous depressions. This indicates that endogenous depressions, while indistinguishable in psychopathological terms, are actually two separate biochemical disorders: one resulting from a 5-HT deficiency and the other from a NA deficiency. Studies of tricyclic antidepressants in combination with monoamine oxidase inhibitors (MAOI), CNS stimulants, or reserpine; MAOI in combination with reserpine; 4-chloro-N-methylamphetamine; 4-chloramphetamine, thyrotropin releasing hormone; and neuroleptics have failed to produce unequivocal findings of a relationship between biochemical and therapeutic effects. Studies of the influence on the monoaminergic systems in humans and animals of therapies with an established effect on mood regulation (electroconvulsive therapy and lithium) have revealed an influence that is too complex to permit analysis in terms of the MA hypothesis.

003718 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Reduced CA-ergic transmission and clinical effects of neuroleptics.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 203-210).

Possible correlations between the therapeutic effects and motor side effects of neuroleptic drugs and their ability to reduce catecholaminergic transmission by receptor block are discussed. The significance of inhibition of noradrenergic transmission in the therapeutic effect of neuroleptics has not been determined. Promethazine, a phenothiazine having sedative but not neuroleptic properties, as well as neuroleptic phenothiazines, increases noradrenalin turnover, suggesting that this effect may be related to the sedative effects of these drugs. Other studies in both animals and humans have suggested that therapeutic effect may be related to dopamine (DA) receptor block. A ranking of neuroleptics according to their ability to inhibit DA transmission roughly corresponds with their ranking according to average clinical doses used. It

has also been shown that the ability of a neuroleptic to increase baseline concentrations and postprobenecid accumulation of homovanillic acid (HVA) in cerebrospinal fluid (indications of increases in DA turnover) are positively correlated with the therapeutic efficacy, both in sedative and antipsychotic terms, of the medication. The occurrence of hypokinetic/rigid side-effects in humans are also positively correlated with the increase in HVA accumulation after probenecid. Neuroleptic induced hyperkinesias and dyskinesias have not been studied in this respect. It is concluded that the data indicate that changes in central DA metabolism are involved in the production of both the therapeutic and side-effects of neuroleptic drugs.

003719 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Testing the DA hypothesis with the aid of drugs.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 219-226).

Studies of the ability of known dopamine (DA) receptor agonists to produce psychoses or aggravate existing psychoses are reviewed and discussed in terms of the DA hypothesis. This hypothesis proposes that dopaminergic hyperactivity is involved in the pathogenesis of schizophrenic psychoses. Amphetamines produce psychosis in healthy subjects given large doses of the stimulants. Evidence that DA hyperstimulation is involved in the pathogenesis of amphetamine psychosis includes: 1) substances which block DA transmission, such as neuroleptics, produce a favorable effect in amphetamine psychoses while other sedatives such as barbiturates do not; 2) stereotyped behavior, a dopaminergically mediated effect of amphetamines in animals, occurs in amphetamine psychoses; 3) amphetamine produces a marked increase in postprobenecid homovanillic acid accumulation (an indication of increased DA turnover) but not of 3-methoxy-4-hydroxyphenylglycol (an indication of central NA turnover) in cerebrospinal fluid; and 4) amphetamine-like psychoses are also produced by cocaine, which also inhibits reuptake of catecholamines (CA). Amphetamines and related stimulants aggravate existing symptoms in schizophrenic patients. L-DOPA, also a DA agonist, can induce psychotic symptoms, but these are variable and generally unlike those of amphetamine psychosis. However, L-DOPA also increases the existing pathology in schizophrenic patients. Alpha-methylparatyrosine, which probably inhibits activity in CA systems by inhibition of CA synthesis, potentiates the pyramidal side-effects of neuroleptics in schizophrenic patients. These data seem to support the DA hypothesis. However, propranolol, a beta-adrenergic blocker which is believed to affect central noradrenalin (NA) receptors but not DA receptors, has an antipsychotic effect. It is suggested that the NA system as a factor in the pathogenesis of psychoses and in their treatment deserves more attention than it has received.

003720 van Praag, Herman M. Department of Biological Psychiatry, State University Groningen, Groningen, The Netherlands **The significance of the cerebral dopamine metabolism in the pathogenesis and treatment of psychotic disorders.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 1-26).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December, 1975, the significance of cerebral dopamine (DA) metabolism in the pathogenesis and treatment of psychotic disorders is discussed. Animal experiments have demonstrated the likelihood that all known neuroleptic drugs inhibit transmission in central catecholaminergic systems, regardless of their chemical structure and the specific mechanisms involved. The ratio of DA receptor blocking activity to noradrenalin (NA) blocking activity differs from one neuroleptic to the next. Studies in humans have revealed that: 1) neuroleptics of the receptor blocking type (i.e. phenothiazines and butyrophenones) increase the probenecid induced accumulation of homovanillic acid (HVA) in the cerebrospinal fluid (CSF), indicating an increase in central DA turnover; 2) neuroleptics increase prolactin levels in blood and CSF, indicating that transmission in central dopaminergic neurons is diminished; 3) there is a positive correlation between clinical improvement in patients with schizophrenic psychoses and the increase in probenecid induced HVA accumulation in CSF; 4) there is a positive correlation between the occurrence of Parkinsonlike hypokinetic/rigid symptoms and the HVA response, with patients having a low pretherapeutic DA turnover being more susceptible to these side-effects; and 5) the extent to which a neuroleptic blocks DA transmission and/or NA transmission is highly predictive of its clinical actions. It is posited that the hypothesis that DA hyperactivity is an important pathogenic mechanism in schizophrenic psychoses is based on indirect arguments, since direct studies of DA metabolism in schizophrenics have failed to provide evidence of a metabolic defect. The possible causes of this failure are discussed. The importance of differentiating between etiological and pathogenetic factors in studying the origin of behavior disorders is emphasized. 57 references.

003721 Verghese, Abraham; Indrani, N.; Kuruvilla, K.; Hill, Peter, G. Christian Medical College, Vellore, India **Usefulness of saliva lithium estimation.** British Journal of Psychiatry. 130:148-150, 1977.

Lithium estimations performed on 24 samples of serum and saliva, taken from ten patients receiving lithium carbonate for affective disorders, showed high correlation between the lithium levels in serum and saliva. Further, estimation of lithium in saliva at different periods of time showed stability for saliva lithium levels. It is concluded that saliva lithium levels are reliable indicators in monitoring lithium treatment and can be used as a substitute for serum for lithium monitoring. 10 references. (Author abstract modified)

003722 Winokur, Andrew. Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104 **Hypothalamic releasing hormones and behavior.** In: Brady, J., Psychiatry: areas of promise and advancement. New York, Spectrum, 1977. 253 p. (p. 65-71).

To illustrate the application of neuroendocrine techniques which may provide data of relevance to such clinical disorders as schizophrenia or depression, the behavioral implications of thyrotropin releasing hormone (TRH) and other hypothalamic releasing hormones is discussed. Development of radioimmunoassay procedure for TRH led to a number of investigations which indicated that TRH may potentiate pharmacological antidepressant effects, may have mood elevating effects itself, and is a potent releasing agent for prolactin. Further studies have suggested that TRH response may serve as an indicator of adequate response to antidepressant therapy. It has been hypothesized that TRH may act in some manner to modify the activity of the neurotransmitters or may itself be a central nervous system neurotransmitter agent, and a number of studies have produced results compatible with this hypothesis. It is concluded that further research on the hypothalamic releasing hormones is needed, and could provide information with considerable practical therapeutic application. 24 references.

003723 Ziegler, Vincent E.; Co, Bun Tee; Biggs, John T. Department of Psychiatry, Washington University School of Medicine, 4940 Audubon Ave., St. Louis, MO 63110 **Plasma nortriptyline levels and ECG findings.** American Journal of Psychiatry. 134(4):441-443, 1977.

To examine the effect of therapeutic doses of nortriptyline on routine ECGs and to determine whether any electrocardiograph (ECG) changes correlated with plasma nortriptyline levels, 17 depressed patients were administered 50 to 150mg nortriptyline per day for a minimum of 3 weeks. ECGs were administered prior to treatment and after treatment. ECG changes were not dramatic. Results did indicate a weak positive correlation between pulse rate and nortriptyline level. Clinicians using nortriptyline who do not have plasma tricyclic assays available may find it useful to take a baseline pulse. The dosage of nortriptyline can be reduced if the pulse rate increases more than 20 bpm during treatment and the patient is not responding to therapy. 8 references.

14 MECHANISM OF ACTION: BEHAVIORAL

003724 Castelden, C. M.; George, C. F.; Marcer, D.; Hallett, C. Faculty of Medicine, University of Southampton, Southampton SO9 3TU, England **Increased sensitivity to nitrazepam in old age.** British Medical Journal (London). No. 6052:10-12, 1977.

The effects of a single 10mg oral dose of nitrazepam were compared with those of a placebo in healthy young and old people to determine if there is increased sensitivity to nitrazepam in old age. Both the young and the elderly slept better on three successive nights after nitrazepam but felt less awake at 12 and 36 hours. Elderly people made significantly more mistakes in a psychomotor test than did the young, despite similar plasma concentrations of nitrazepam and half lives in the two groups. This difference in response to psychomotor testing is probably explained by an increased sensitivity of the aging brain to the action of nitrazepam. 23 references. (Author abstract modified)

003725 Ghoneim, M. M.; Mewaldt, S. P. Dept. of Anesthesia, University of Iowa, Iowa City, IA 52242 **Studies on human memory: the interactions of diazepam, scopolamine, and physostigmine.** Psychopharmacology (Berlin). 52(1):1-6, 1977.

Seventy volunteers were injected with diazepam (0.3mg/kg), scopolamine (8 microgm/kg), or placebo, followed 70 min later by injection of physostigmine, physostigmine and methscopolamine (in the case of diazepam treatment), or placebo to investigate the effects of these drugs on human memory. Subjects were tested in groups of five in a double-blind procedure with treatments distributed according to a Latin square design. Prior to treatment, Ss heard a series of lists of words, followed by an immediate recall test. Following the first injection, delayed free recall and recognition tests were given. The second drug was then injected, followed by a presentation of another two sets of lists which were tested similarly. Subjective feelings were also evaluated with a rating questionnaire. Diazepam and scopolamine did not affect recall of information which had been learned prior to drug injection. However, both drugs impaired the learning or acquistion of new information. Physostigmine antagonized most of the memory deficits produced by scopolamine while those of diazepam remained. It is suggested that scopolamine acts centrally through an anticholinergic mechanism while diazepam may act through a different system. 20 references. (Author abstract modified)

003726 Gibson, H. B.; Corcoran, M. E.; Curran, J. D. Hatfield Polytechnic, P.O. Box 109, Hatfield, Herts AL10 9AB, England **Hypnotic susceptibility and personality: the consequences of diazepam and the sex of the subjects.** British Journal of Psychology (London). 68(1):51-59, 1977.

A hypothesis of the relationship between hypnotic susceptibility and the personality parameters of extraversion and neuroticism was tested. The test-retest data for hypnotic susceptibility was reported for 71 subjects, half of whom were retested after receiving diazepam and half after receiving nicotinic acid (placebo). The hypothesis that a tranquilizing drug would raise the susceptibility of neurotic extraverts and lower that of neurotic introverts was confirmed. The significance of drugs in different aspects of hypnotic susceptibility in relation to personality is discussed. 15 references. (Author abstract modified)

003727 Gillin, J. Christian; van Kammen, Daniel P.; Post, Robert; Bunney, William E., Jr. Unit on Sleep Studies, APB, NIMH, Bldg. 10, Room 3N224, Bethesda, MD 20014 **Effects of prolonged administration of pimozide on sleep-EEG patterns in psychiatric patients. (Unpublished paper).** Bethesda, MD, NIMH, 1977. 7 p.

To determine the effects of pimozide, a potentially useful tool for determining the role of dopamine in sleep/wakefulness and in schizophrenia, on sleep, EEG sleep patterns and nurses' ratings of behavior were studied before, during, and after a clinical trial of pimozide in 10 psychiatric inpatients with varying diagnoses. Total Sleep Time, Sleep Efficiency, and Stage II (both minutes per night as a percentage of Total Sleep time) were significantly increased during treatment with pimozide as compared with baseline before treatment and withdrawal afterwards. 9 references. (Author abstract)

003728 Gillis, John S. Oregon State University, Corvallis, OR 97331 **The effects of selected antipsychotic drugs on human judgment.** Current Therapeutic Research. 21(2):224-232, 1977.

The effects of three commonly used antipsychotic agents, haloperidol, trifluoperazine, and thioridazine, were evaluated on a series of judgment tasks of graduated complexity. Subjects were 26 hospitalized chronic schizophrenics selected for inclusion in the study on the basis of their present chemotherapeutic regimens. Judgmental performance was evaluated in terms of overall adequacy and its component indices of knowledge and cognitive control. Patients receiving haloperidol and trifluoperazine were superior to those receiving thioridazine on all indices, these differences being significant on the measure of overall performance. Differences appeared attributable to the inability of thioridazine subjects to make effective use of detailed feedback. 11 references. (Author abstract modified)

003729 Goodman, R. E. no address **The management of premature ejaculation.** Journal of International Medical Research (Northampton). 5(Supplement 1):78-79, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the use of clomipramine and behavioral procedures in the treatment of premature ejaculation are discussed. The types of men presenting with this problem and the difficulties associated with treatment are considered. A rational approach to therapy based on age, physical condition, and psychological difficulties is presented. 7 references. (Journal abstract modified)

003730 Gottschalk, Louis A.; Aronow, Wilbert S.; Prakash, Ravi. Department of Psychiatry, College of Medicine, University of California at Irvine, Irvine, CA **Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological cardiovascular functioning in anginal patients.** Biological Psychiatry. 12(2):255-266, 1977.

A study of the acute effects of smoking marihuana on cognitive and emotional reactions and on cardiovascular function is presented. Ten male anginal patients with angiographically documented coronary artery disease, in a randomized double-blind crossover study, smoked one marihuana cigarette on one morning and one placebo marihuana cigarette on a successive morning. Significant increases occurred in average cognitive and intellectual impairment scores, derived from content analysis of 5 min of speech, 30 mins after smoking the marihuana cigarette as compared to the placebo, and these scores decreased to near presmoking levels 60 min after smoking. No significant average changes occurred in anxiety or three hostility scale scores following smoking marihuana. Sizable differences were noted in psychological responses to marihuana smoking due, presumably, to personality differences or differences in THC pharmacokinetics. Significant psychocardiovascular hemodynamic correlations, as measured by echocardiography, were observed during placebo marihuana smoking and these were all eliminated during marihuana smoking. In view of associated findings that marihuana smoking decreased myocardial oxygen delivery, decreased exercise time until the onset of anginal pain, and increased myocardial oxygen demand in anginal patients, the use of marihuana by such patients is clearly inadvisable. 46 references. (Author abstract)

003731 Greenblatt, David J.; Shader, Richard I.; Harmatz, Jerold S.; Franke, Kate; Koch-Weser, Jan. Analytical Laboratory, Clinical Pharmacology Unit, Massachusetts General Hospital, Boston, MA 02114 **Absorption rate, blood concentrations, and early response to oral chlordiazepoxide.** American Journal of Psychiatry. 134(5):559-562, 1977.

Absorption rate, blood concentrations, and early response to oral chlordiazepoxide (CDX) were studied to test the hypothesis that differences in rate of drug absorption can influence the clinical response to single doses of antianxiety agents. Ten healthy male subjects received CDX hydrochloride or matching placebo with Maalox or water in a four way single dose crossover trial. Coadministration of CDX with Maalox did not change the completeness of CDX absorption but significantly slowed its rate of absorption and the rate of desmethylchlordiazepoxide (DMCDX) appearance. Self-ratings of feeling "spacey" at 1.0and 2.5hours were significantly increased over baseline for CDX taken with water but not with Maalox. Increases in "spacey" feelings at 1.0hours were highly correlated with 0.5hour but not with 1.0hour blood levels. Similar findings were observed for self-ratings of "thinking slowed down." Certain subjective effects of antianxiety agents after oral dosage may depend on the rate of drug absorption and may be attenuated or eliminated if the absorption rate is reduced. 10 references. (Author abstract modified)

003732 Grinspoon, Lester; Bakalar, James B. Massachusetts Mental Health Center, Boston, MA **A kick from cocaine.** Psychology Today. 10(10):41-42, 78, 1977.

A brief review of the physical, social and psychological effects of cocaine use, based on the limited amount of available research and on interviews with cocaine users is presented. Cocaine, when taken orally or sniffed, produces a mild euphoric state briefer and milder than the state produced by amphetamines. Like other stimulants, cocaine often produces a feeling of improved physical and intellectual capacity; and some studies have indicated that cocaine improves speed, attention and reaction time on simple mental tasks. In large doses, cocaine can produce delusions of grandeur and paranoia, but no evidence exists linking cocaine use to chronic psychosis. Physiologic effects of cocaine include anesthetization, and increases in pulse rate, breathing, body temperature and blood sugar levels. In excessive doses, cocaine may produce headache, hyperventilation, nausea, vertigo, convulsions, and even death. Although cocaine has some reputation as an aphrodisiac, the relationship between sex and psychoactive drugs is obscure. An indirect link may exist between cocaine use and aggression, but due to the relatively mild and transient effects of the drug, it is less likely to cause violence than many other more commonly used drugs. While not addictive, withdrawal from cocaine after long-term use may be associated with the same sort of dependency associated with nicotine or caffein use.

003733 Janowsky, David S.; Huey, Leighton; Storms, Lowell; Judd, Lewis L. Department of Psychiatry, University of San Diego School of Medicine, La Jolla, CA 92037 **Methylphenidate hydrochloride effects on psychological tests in acute schizophrenic and nonpsychotic patients.** Archives of General Psychiatry. 34(2):189-194, 1977.

Actively psychotic schizophrenic and nonpsychotic psychiatric inpatients received intravenous methylphenidate hydrochloride to determine whether psychostimulants can cause a genuine increase in psychotic thinking or whether psychosis activation is merely an artifact due to increased patient verbalization. Each patient was rated for level of psychosis and talkativeness, and each received the Holtzman projective ink blot tests and the Kent-Rosanoff word association tests before, during, and after methylphenidate infusion. Minnesota Multiphasic Personality Inventory Goldberg Index scores were also obtained as a general measure of psychosis. For the entire patient group, methylphenidate infusion was followed by a significant increase in talkativeness and psychosis ratings and in pathological responses to the Holtzman ink blot test. There was a significant decrease in common word associations. Since neither of the psychological tests allow more than one response per item, it appears that methylphenidate truly effects pathological thought processes and decreases common word associations as such, rather than merely making these processes more evident by increasing verbalization. 17 references. (Author abstract modified)

003734 Judd, Lewis L.; Hubbard, R. Bruce; Huey, Leighton Y.; Attewell, Paul A.; Janowsky, David S.; Takahashi, Kenneth I. Department of Psychiatry, M-003, School of Medicine, University of California, San Diego, La Jolla, CA 92093 **Lithium carbonate and ethanol induced "highs" in normal subjects.** Archives of General Psychiatry. 34(4):463-467, 1977.

The responses of 23 normal male subjects to a standardized dose of 95% ethanol were compared after 2 weeks of placebo and 2 weeks of therapeutic serum lithium ion levels. The study was a placebo controlled, split-half crossover, double-blind design. Prealcohol and postalcohol responses were assessed by self-rating scales of affect and mood, independent rater observation, perceptomotor, and cognitive performance tasks. Pretreatment by lithium carbonate neither blocked nor dampened an alcohol induced subjective "high" in normal subjects. A complex reciprocal interaction may exist between the effects of lithium and alcohol upon other behavioral attributes.

Alcohol was seen to reverse aspects of lithium induced dysphoria, and there is a suggestion that lithium may attenuate alcohol induced cognitive inefficiency. 11 references. (Author abstract)

003735 Judd, Lewis L.; Hubbard, Bruce; Janowsky, David S.; Huey, Leighton Y.; Attewell, Paul A. Department of Psychiatry, M-003, School of Medicine, University of California, San Diego, La Jolla, CA 92093 **The effect of lithium carbonate on affect, mood, and personality of normal subjects.** Archives of General Psychiatry. 34(3):346-351, 1977.

To study effects of lithium carbonate, data reflecting affect, mood, and personality attributes of 23 normal men were compared after 2 weeks of placebo administration and 2 weeks of therapeutic serum lithium levels. The study was a placebo controlled, split half crossover, double-blind design. Affect and mood were measured by three self-rating instruments, by independent rater observation, and by the subjects' "significant others." Two personality inventories were administered. Substantial affect and mood changes were induced by lithium carbonate. Lethargy, dysphoria, a loss of interest in interacting with others and the environment, and a state of increased mental confusion were reported. No generalized effects were found in the responses to the personality inventories. 23 references. (Author abstract)

003736 Judd, Lewis L.; Hubbard, Bruce; Janowsky, David S.; Huey, Leighton Y.; Takahashi, Kenneth I. Department of Psychiatry, M-003, School of Medicine, University of California, San Diego, La Jolla, CA 92093 **The effect of lithium carbonate on the cognitive functions of normal subjects.** Archives of General Psychiatry. 34(3):355-357, 1977.

The responses of 24 normal male subjects were compared after 2 weeks of lithium carbonate administration on a series of tasks of intellectual function, aesthetic judgment, and semantic creativity. This was a placebo controlled, split half crossover, double-blind design. There were no significant changes on semantic creativity or aesthetic perception measures following lithium carbonate maintenance. There were lithium carbonate related performance deficits on three of five performance tasks concerned with cognitive and/or motor functions. The deficit is probably due to a lithium carbonate induced slowing of performance, consistent with previous reports of subjective effects in normal subjects. The implications of slowing on possible behavioral mediating mechanisms by which lithium carbonate exerts its clinical effects are discussed. 10 references. (Author abstract)

003737 Kales, Anthony; Bixler, Edward O.; Kales, Joyce D.; Scharf, Martin B. Sleep Research and Treatment Center, Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, PA **Comparative effectiveness of nine hypnotic drugs: sleep laboratory studies.** Journal of Clinical Pharmacology. 17(4):207-213, 1977.

The comparative effectiveness of nine hypnotic drugs: 1000mg chloral hydrate (Noctec); 500mg ethchlorvynol (Placidyl); 30mg flurazepam (Dalmane); 500mg glutethimide (Doriden); 250mg and 400mg methaqualone (Parest); 100mg secobarbital (Seconal); 100mg GP 41299 (a dibenzothiepine derivative); and 0.5mg triazolam (U33030, a benzodiazepine) in 4 insomniac subjects were examined in sleep laboratory studies. The subjects were given a placebo on each of the first 4 nights to study baseline values, the test drug for 14 nights to study drug effectiveness over time, and a placebo for each of the last 4 nights to study withdrawal effects. The middle 8 nights of test drug administration, the subject spent in his home. On each laboratory night, electroencephalogram, electromyogram, and electrooculogram measurements were taken for 8 hr. All the drugs were relatively effective in improving sleep with initial and short-term use. With intermediate term use (2 wk), all except flurazepam showed a marked decrease in effectiveness. Following withdrawal, sleep was similar to baseline with most of the drugs, continued to be improved with flurazepam, and worsened beyond baseline levels with triazolam. 10 references.

003738 Kristensen, V.; Olsen, M.; Theilgaard, A. Laegehuset, Ellenmarksvej, 4600 Koge, Kobenhavn, Denmark **Levodopa treatment in presenile dementia.** Acta Psychiatrica Scandinavica (Kobenhaven). 55(1):41-51, 1977.

Levodopa treatment presenile dementia was investigated to determine whether cognitive dysfunction and psychopathological symptoms in the presenile demented patient are influenced by L-dopa substitution. In Parkinson's disease as well as presenile dementia there is a dopamine deficit in the basal ganglia. Extrapyramidal symptoms are common in presenile dementia, and dementia is a common trait in Parkinsonism. It is reasonable to suggest a partial common etiology and pathophysiology, and the logical consequence is an investigation of levodopa substitution in presenile dementia. Previous investigations have been uncontrolled or carried out on small or inhomogeneous materials. A triple-blind clinically controlled investigation in which the material is very homogeneous was undertaken. After 6 months' levodopa treatment no significant effect is shown either on a broad spectrum of psychiatric items or in cognitive functioning. This negative result is discussed. The probability of a specific Parkinson dementia is mentioned and the significance of the modifying effect of an imbalance in other transmitter systems is emphasized. 30 references. (Author abstract)

003739 Malhotra, H. K.; Olgiati, S. G. Department of Psychiatry, College of Medicine and Dentistry of New Jersey, Newark, NJ 07107 **Fluphenazine therapy in groups.** Comprehensive Psychiatry. 18(1):89-92, 1977.

Initial observations on the formation of a fluphenazine treatment group at the Psychiatric Clinic of Newark Beth Israel Medical Center are reported. It was found that the group helped the individual to recognize the nature and management of side-effects. The subjective reaction of patients and family members was improved to the extent that more patients were willing to continue injections in spite of the higher frequency of side-effects. Patients attributed past psychotic episodes to their inability to take oral medication. The class method reported by Pratt in 1907 was found useful in the treatment of chronic schizophrenics. 16 references.

003740 Mamelak, Morty; Escriu, Joseph M.; Stokan, Olga. Sunnybrook Medical Center, University of Toronto Clinic, Toronto, Ontario, Canada **The effects of gamma-hydroxybutyrate on sleep.** Biological Psychiatry. 12(2):273-288, 1977.

A report on the preliminary testing of the drug sodium gamma-hydroxybutyrate (GHB), a hypnotic and a normal metabolite of the mammalian nervous system, on eight patients with histories of impaired sleep, is presented. Sleep induced with GHB was indistinguishable subjectively from natural sleep as well as by behavioral and electroencephalographic criteria. Unlike most synthetic hypnotics, GHB increased delta sleep and did not suppress REM sleep. It shortened the REM sleep latency and shifted REM sleep into the first third of the night. On one occasion it induced a sleep onset REM period which was experienced as an attack of sleep paralysis.

Withdrawal was simple; there was no REM sleep rebound and sleep patterns immediately returned to their predrug form. Its major clinical drawback was its short duration of action: its hypnotic effect lasting only 2 to 3 hr. It is suggested that GHB may serve as the prototype for a new class of hypnotic compounds derived from natural sources and capable of activating the neurological mechanisms of normal human sleep. 37 references. (Author abstract)

003741 Marini, J. L.; Sheard, M. H. 34 Park Street, New Haven, CT 06508 **Antiaggressive effect of lithium ion in man.** Acta Psychiatrica Scandinavica (Kobenhavn). 55(4):269-286, 1977.

Key issues in lithium research on human aggression, problems in defining aggression and data suggesting an antiaggressive effect of lithium are reviewed. It is suggested that aggression should be related to easily identifiable behavior: angry threats or actual assaults, and that aspects of behavior not meeting these criteria but relevant to a study of aggression should be described using appropriate terms such as social dominance and initiative. With these conventions, examination of the heterogeneous literature on lithium treatment of aggression demonstates that lithium ion exerts an antiagressive effect in man. A number of hypotheses for the antiagressive effect are examined using previous studies and new behavioral and biochemical data. It is concluded that the antiaggressive effect is not due to any of the following: lithium toxicity or side effects; subjective or objective weakness; increased reaction time; reduced coordination or motor performance; frank cognitive deficits; hypothyroidism; reduction of serum testosterone; placebo effect; or underlying manic-depressive illness. Putative thymoleptic properties of lithium are too ambiguous to constitute an explanation of lithium's actions in man. 35 references. (Author abstract)

003742 Marshall, A. J.; Barritt, d. w.; Pocock, Jessica, Heaton, Susan. Bristol Royal Infirmary, Bristol BS2 8HW England **Evaluation of beta blockade, bendrofluazide, and prazosin in severe hypertension.** Lancet (London). No. 8006:271-274, 1977.

In a within patient comparison of two drug regimens, 20 patients with severe essential hypertension who had an inadequate fall in blood pressure with beta blockade alone, were given in random order either 5mg or 10mg of bendrofluazide a day or prazosin 2mg three times daily rising to 5mg if required. Ten patients who did not achieve a satisfactory fall in pressure with either agent were then given all three drugs together. When bendrofluazide 5 or 10mg was added to beta-blockade there was average fall in mean blood pressure, standing, of 13%. When prazosin was added to beta blockade the average fall in mean blood pressure, standing, was 16%. Eighteen patients who completed the trial had an average final blood pressure, standing, of 139/93mm Hg. In the prazosin period eight patients continued to complain of dizziness after the first 24 hr. With bendrofluazide serum potassium levels fell below 3.6mmol/l in half the patients within the first 2 weeks of treatment. It is concluded that patients with essential hypertension already treated with beta blockade who need an additional agent will get a further fall in blood pressure with 5mg of bendrofluazide. Prazosin appears to be a potent and appropriate third agent. 6 references. (Author abstract modified)

003743 Miller, L. L.; Cornett, T. L.; Brightwell, D. R.; McFarland, D. J.; Drew, W. G.; Wikler, A. Dept. of Psychiatry, University of Kentucky Medical Center, Lexington, KY 40506 **Marijuana: effects on storage and retrieval of prose material.** Psychopharmacology (Berlin). 51(3):311-316, 1977.

In a two phase design, an attempt was made to differentiate the effect of marihuana on the storage and retrieval of prose material in 40 moderate smokers of marihuana. In the first phase, the subjects smoked a single 500mg marihuana cigarette containing 2.1% delta9-tetrahydrocannabinol or a placebo cigarette, and 15 minutes later listened to and at the same time read a narrative passage of approximately 200 words. An immediate free recall test was given in which the subjects were asked to write down as much as they could remember. In the second phase, 24 hours later, the subjects smoked marihuana or placebo cigarettes and 15 minutes later were asked questions concerning facts and events from the passage given the day before and were then given a new prose passage. Results indicated that marihuana reduced immediate recall under both cued and uncued conditions in comparison to placebo. No relative cued recall advantage was found in the marihuana groups for the old or new story and marihuana produced only a moderate decrement in recall of the old story on the second day. However, marihuana given in the second phase significantly reduced memory for items recalled in the first phase irrespective of drug or cueing conditions in phase one, suggesting that retrieval was also affected. There was some suggestion that cueing differentially influenced the shape of the serial position curve during recall of the old story, but this effect was marginal. 14 references. (Author abstract modified)

003744 Nash, Ralph J.; Wittenborn, J. R.; Flaherty, Charles F. Rutgers Interdisciplinary Research Center, Rutgers-The State University, New Brunswick, NJ 08903 **Psychomotor procedures to distinguish between antidepressant medications: a comparison of the effects of nomifensine maleate, imipramine HCl, and placebo on the psychomotor performance of normal males.** Psychopharmacology Bulletin. 13(2):54-55, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, the psychomotor performances of 90 male volunteers were tested after the administration of nomifensine maleate, imipramine HCl, or placebo in a double-blind study. The subjects were tested hourly in 30 min testing sessions with the Digit Symbol Substitution Test, a Perceptual Reversal (Necker Cube) Judgment of a Temporal Interval, and Simple and Complex Vigilance Tests, both of which required recognition of briefly exposed letters of the alphabet. Relative to placebo or nomifensine maleate, imipramine HCl had a clearly detracting effect on most of the tests. Drowsiness was reported more often in the imipramine group than in the other two groups.

003745 Resnick, Richard B.; Kestenbaum, Richard S.; Washton, Arnold; Poole, Doris. Department of Psychiatry, New York Medical College, 5 E. 102nd St., New York, NY 10029 **Naloxone-precipitated withdrawal: a method for rapid induction onto naltrexone.** Clinical Pharmacology and Therapeutics. 21(4):409-413, 1977.

Naloxone precipitated withdrawal was examined as a means for rapid opiate detoxification and induction onto naltrexone. In 29 patients dependent on methadone (5 to 20mg/day), abstinence was precipitated by an injection of naloxone. Repeated injections of naloxone were given subsequently until symptoms of abstinence were no longer induced. Successive injections induced less intense drug withdrawal assessed by vital signs and ratings on abstinence scales. The most rapid procedure consisted of 1.2mg naloxone every 30 min for 3 to 6 hr followed by hourly increasing doses of naltrexone. This procedure allowed transition from opiate dependence to nal-

trexone maintenance within 48 hr. The results are consistent with assumptions that antagonists actively displace opiates from receptor sites. 6 references. (Author abstract)

003746 Rossi, A. Michael; Kuehnle, John C.; Mendelson, Jack H. Alcohol and Drug Abuse Research Center, Harvard Medical School, McLean Hospital, Belmont, MA 02178 **Effects of marihuana on reaction time and short-term memory in human volunteers.** Pharmacology Biochemistry and Behavior. 6(1):73-77, 1977.

Twenty seven adult male marihuana smokers volunteered to participate in a hospital research ward study for a 31 day period to study the effects of marihuana on reaction and short-term memory. Following five days of baseline acclimatization, subjects could purchase and smoke marihuana cigarettes on a free choice basis for a period of 21 consecutive days. The marihuana smoking period was followed by a concluding five day baseline. Measurements of simple reaction time, choice reaction time and short-term memory were carried out during the entire study. Analysis of variance revealed no statistically significant differences between control and marihuana performance; however, a correlational analysis showed that individual subject performances on all three tasks were significantly correlated from test session to test session during control conditions but not during marihuana smoking conditions. Findings are discussed in relation to attentional and motivational factors associated with performance on the three tasks. 32 references. (Journal abstract modified)

003747 Schain, Richard J.; Ward, Joseph W.; Guthrie, Donald. Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA 90024 **Carbamazepine as an anticonvulsant in children.** Neurology. 27(5):476-480, 1977.

To evaluate the effect of carbamazepine, a tricyclic compound related to imipramine, on the cognitive function of children with motor or psychomotor convulsive disorders, 45 children 5 1/2 to 15 years old were treated with carbamazepine in place of sedative anticonvulsants (phenobarbital, primidone) because of chronic behavioral difficulties. A battery of measures believed to reflect attentional and perceptual abilities was administered initially and repeated 4 to 6 months later following the drug crossover. At the conclusion of the study, 37 of the 45 children were judged to be drug successes; that is, general alertness and attentiveness were improved, while seizures were adequately controlled. This study indicates that therapeutic regimens of carbamazepine are less likely to interfere with mental functions in children than are equivalent doses of sedative anticonvulsants. 23 references. (Author abstract)

003748 Schmidt, Helmut S.; Clark, Robert W.; Hyman, Paul R. College of Medicine, Ohio State University, Columbus, OH 43210 **Protriptyline: an effective agent in the treatment of the narcolepsy-cataplexy syndrome and hypersomnia.** American Journal of Psychiatry. 134(2):183-185, 1977.

Protriptyline is presented as an effective agent in the treatment of the narcolepsy/cataplexy syndrome and hypersomnia. Five case reports illustrate that 10 to 20mg of protriptyline in a single dose at bedtime can effectively control arousal dysfunction and the narcolepsy/cataplexy syndrome without the apparent development of tolerance and without the side-effects that are frequent complications of treatment agents. Although protriptyline was efficacious in controlling symptoms, it was found to have relatively poor REM sleep suppressing properties. 11 references. (Author abstract modified)

003749 Sitaram, Natarajan; Mendelson, Wallace B.; Wyatt, Richard Jed; Gillin, J. Christian. Adult Psychiatry Branch, Div. of Clinical and Behavioral Research, NIMH, Bethesda, MD 20014 **The time-dependent induction of REM sleep and arousal by physostigmine infusion during normal human sleep.** Brain Research (Amsterdam). 122(3):562-567, 1977.

The effects of physostigmine (P) infusion during normal sleep were studied in humans (N=33) to evaluate the time and dose dependent induction of rapid eye movement (REM) sleep and arousal. Infusion of 0.5mg at 5 min and 35 min after sleep onset significantly reduced the time from infusion to onset of the first REM period compared to placebo. In contrast, the same dose of P given at REM onset and during the second nonREM period caused awakening. Infusion of 0.25mg P 25 min after the end of the first REM period induced REM sleep without awakening the subjects. It is suggested that cholinergic mechanisms are involved in both the induction of REM sleep and behavioral arousal. 10 references.

003750 Small, J. G.; Small, I. F.; Milstein, V.; Dian, D. A. Larue D. Carter Mem. Hosp., Indiana Univ. School of Med., 1315 W. 10th St., Indianapolis, IN 46202 **Effects of ACTH 4-10 on ECT-induced memory dysfunctions.** Acta Psychiatrica Scandinavica (Kobenhavn). 55(4):241-250, 1977.

Two double-blind studies of ACTH 4-10 and placebo were conducted in psychiatric patients (n=29, n=30) receiving bilaterial ECT to determine whether the polypeptide exerted antiamnesic effects. Observations after a single ECT were suggestive of some positive effects, but studies between seizures after five or six ECTs showed no significant drug placebo differences. Although the findings were largely negative, they do not rule out positive effects of ACTH 4-10 on memory. Possibly the designs and timing of the experiments and/or the dosages of ACTH 4-10 employed were unsuitable for demonstrating such influences. 29 references. (Author abstract)

003751 Tecce, Joseph J.; Cole, Jonathan O.; Mayer, Joseph; Lewis, David C. Laboratory of Neuropsychology, Boston State Hospital, Boston, MA 02124 **Barbiturate effects on brain function (CNV) and attention performance in normal men.** Psychopharmacology Bulletin. 13(2):64-66, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, the effects of phenobarbital and pentobarbital on brain functioning (contingent negative variance) (CNV) and attention performance were studied in 30 male volunteers. CNV was recorded from frontal, central, and parietal (Pz) scalp areas referenced to linked earlobes. Two types of CNV based on fast (type A) and slow (type B) rise times were noted. In the 2nd hr posttreatment, the phenobarbital group showed a significantly lower amplitude of CNV recorded at PZ than did the placebo group and tended to be slower in the Continuous Performance Test (CPT). The barbiturates had no significant effects on CNV amplitudes under other conditions. An elevation in dysphoria scores in the phenobarbital group suggests that CNV reduction at Pz and attention performance decrement on the CPT may have been mediated by distraction from a negative hedonic mood state. This may be one reason why this barbiturate is less abuse prone than pentobarbital. Subjects with a type B CNV shape, but not type A individuals, showed slower discrimination latencies in the 2nd and 3rd hours postdrug and appeared to show increased dysphoric mood at those times. Type B individuals may be prone to distraction from a negative hedonic state, such as dysphoria, and these characteristics may be magnified by phenobarbital. 8 references.

003752 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Verification of the MA hypothesis with the aid of drugs: MA precursors and synthesis inhibitors.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 93-106).

Studies of the ability of monoamine (MA) precursors and MA synthesis inhibitors to induce or alleviate symptoms of depression and/or mania are reviewed and discussed in terms of the MA hypothesis. This hypothesis is a combination of the serotonin (5-hydroxytryptamine, 5-HT) hypothesis and the catecholamine (CA) hypothesis which proposes that disturbances in central CA and/or 5-HT metabolism resulting in an absolute or relative deficiency in these substances is involved in the pathogenesis of depressive and manic syndromes. It is noted that studies of 5-HT synthesis stimulants such as tryptophan and 5-hydroxytryptophan, alone or in combination with proven antidepressants, CA synthesis stimulants such as L-DOPA, MA synthesis inhibitors such as alpha-methyl-paratyrosine, methyldopa, fusaric acid, and parachlorophenylalanine have produced equivocal results. However, indications that these substances are not therapeutically inert are too numerous to warrant rejection of this strategy as ineffective and interpretation of the results as evidence against the MA hypothesis. The variability of results may be due to the performance of studies in biochemically undifferentiated groups of depressive patients, and it is posited that MA precursors may be effectively used in certain biochemical subtypes of depression. Research with synthesis blockers indicates that intracerebral dopaminergic hyperactivity is involved in the development of manic symptoms, and that inhibition of CA synthesis promotes motor retardation and possibly decreases in mood level. Inhibition of 5-HT synthesis does not apparently have a depressogenic effect. However, inhibition of 5-HT synthesis arrests the therapeutic effects of tricyclic antidepressants, indicating a relationship between 5-HT and mood regulation.

003753 Van Putten, Theodore; Alban, Jack. Brentwood Veterans Administration Hospital, Wilshire and Sawtelle Blvds., Los Angeles, CA 90073 **Lithium carbonate in personality disorders: a case of hysteria.** Journal of Nervous and Mental Disease. 164(3):218-222, 1977.

A case is reported in which diabolical behavior, conversion symptoms, and diffuse violence and cruelty in a young woman responded remarkably well to treatment with lithium. Blind substitution of a placebo confirmed a lithium effect. Literature on the use of lithium in treatment of some nonmanic depressive disorders is reviewed. It is suggested that patients with the diagnosis of explosive, antisocial, and hysterical personalities would appear to be the best candidates for a trial of lithium. 30 references.

003754 Wang, Richard I. H.; Wilbur, Marjorie; Hieb, Elizabeth. Clinical Pharmacology Section/116E, Veterans Administration Center, Wood, WI 53193 **Determining optimum dose and acute tolerance of triazolam.** Journal of International Medical Research (Northampton). 5(3):184-190, 1977.

A two phase study was designed to determine the optimum hypnotic dose of triazolam and to assess any evidence of acute tolerance. Subjective and objective data were used to assess hypnotic efficacy. In the dose titration phase the triazolam dosage was increased in 0.5mg increments to the highest level tolerated by each patient. Maximum tolerable doses ranged between 0.5and 3.0mg; however, all subjects experienced maximum therapeutic effect at 1.5mg triazolam. During the 4 night acute tolerance portion of the study no clear evidence of tolerance was found. 5 references. (Author abstract modified)

003755 Wedl, W.; Suchenwirth, R. M. A. Neurologische Klinik, Monchebergstr. 41, D-3500 Kassel, Germany **/Effects of the GABA derivative piracetam: a double blind study in healthy probands./** Eigenwirkungen des GABA-Abkommlings Piracetam im doppelten Blindversuch bei gesunden Probanden. Nervenarzt (Berlin). 48(1):58-60, 1977.

The effects of the GABA derivative piracetam were evaluated in a double-blind study involving healthy subjects. Twenty-four subjects were given 3500mg piracetam for 5 days in a double-blind crossover format. Various psychometric tests were administered before and during placebo/medication periods. Results show that learning ability and test performance were significantly improved and that "inner tempo" and mental alertness were increased. 11 references.

003756 Weil, Andrew T. Botanical Museum of Harvard University, Cambridge, MA **/Differences in the experiences of using coca and cocaine./** The green and the white. Journal of Altered States of Consciousness. 2(4):339-359, 1975-76.

Experiences with both coca and cocaine arae described, along with the history, pharmacology, effects, and uses (particularly among South American Indians) of each of the two drug forms. The development of cocaine from the coca leaves is also described, and current American views of cocaine and laws against its use are criticized as both inaccurate and unjustified. Two main problems with the use of cocaine are considered: 1) its fatiguing effects and 2) the tolerance that develops to the drug with increasing use. Advantages of using coca leaves in their original form are discussed (e.g. no tolerance or dependent behavior develops; it is pleasant to consume; and it is moderately stimulating). The usefulness of coca leaves for general physicians in the US is also examined, although problems of supply are pointed out. 6 references.

003757 Welch, Robert B.; Schroeder, David J.; Thurgate, Janet K.; Erickson, Carlton K.; Higgins, Raymond L.; Wait, John S. Department of Psychology, University of Kansas, Lawrence, KS 66045 **The effect of alcoholic intoxication upon calorically induced oculogyral illusion.** Perception and Psychophysics. 21(4):352-356, 1977.

An experiment was conducted to investigate the effects of alcohol upon calorically induced "culogyral illusion" (OGI) and to examine the role of drinking experience in the effects of intoxication. Ten male and ten female subjects, half of whom were classified as heavy and half as light drinkers, ingested a 4:1 combination of tonic water and 80 proof vodka in an amount calculated to produce a state of moderate intoxication (average estimated peak blood alcohol level = .075). This resulted in an increased sensitivity (latency, magnitude, and duration) to the calorically induced "oculogyral illusion" relative to a placebo (tonic water) condition. Heavy and light drinkers did not differ significantly on any of the measures. It was speculated that the alcoholic enhancement of the OGI was due either to a decreased ability to suppress vestibular nystagmus when attempting to fixate a visual stimulus or to the expenditure of extranormal effort in order to maintain fixation. 19 references. (Journal abstract modified)

003758 Yepes, Luis E.; Winsberg, Bertrand G. New York Dept. of Mental Hygiene, Office of Research, Child Psychiatric Evaluation Research Unit, 524 Clarkson Avenue,

Brooklyn, NY 11203 **Vomiting during neuroleptic withdrawal in children.** American Journal of Psychiatry. 134(5):574, 1977.

Two cases of vomiting during neuroleptic withdrawal in children are reported, and reasons are suggested. Both cases involved subjects participating in a project investigating the relationship between extrapyramidal movement disorders and monoamine metabolites in cerebrospinal fluid following neuroleptic withdrawal. In one case vomiting occurred between days 4 and 20 following withdrawal. In the other it occurred intermittently on days 21 through 32. Neuroleptics are known to block the emetic effects of apomorphine, a dopamine (DA) receptor agonist that induces vomiting by its action at the chemoreceptor trigger zone (CTZ) of the medulla. It is suggested that after chronic blockade of the CTZ by neuroleptics, the abrupt withdrawal might be associated with supersensitivity of these DA receptors and the vomiting that results. 4 references. (Author abstract modified)

15 TOXICOLOGY AND SIDE EFFECTS

003759 Adams, Bruce E.; Manoguerra, Anthony S.; Lilja, G. Patrick; Long, Robert S.; Ruiz, Ernest. Ripple River Medical Center, Aitkin, MN **Heat stroke associated with medications having anticholinergic effects.** Minnesota Medicine. 60(2):103-106, 1977.

Cases are presented in which the patients treated for heat stroke were taking medications with anticholinergic properties and in which the high incidence of morbidity and mortality associated with heat stroke are illustrated. In 11 cases of heat stroke treated during July 1974 at Hennepin County Medical Center (Minnesota), eight of the cases involved a patient who was taking medication with anticholinergic properties. Anticholinergic drugs (atropine, scopolamine, propantheline) can interfere with thermoregulation, block the nervous stimuli for sweat gland excretion, and disrupt hypothalamic controls. Suggestions are made for prevention of heat stroke in elderly persons who may be at risk as a result of their medication and of environmental factors. 11 references.

003760 Allen, Robert E.; Stimmel, Glen L. 1934 Hospital Place, Los Angeles, CA 90033 **Neuroleptic dosage, duration, and tardive dyskinesia.** Disease of the Nervous System. 38(5):385-387, 1977.

To illustrate the relationship between neuroleptic dosage and duration, and the reversibility of tardive dyskinesia, case histories of four patients who developed tardive dyskinesia during treatment with either chlorpromazine or haloperidol are presented. In three of the four cases, dyskinesia resolved following withdrawal from medication. In these cases and previously reported cases high dose neuroleptic therapy could not be considered a highly significant factor in the development of tardive dyskenesia, but data suggest that duration of therapy and early detection of symptoms are most important in the development and subsequent reversibility. It is suggested that, while necessary in most schizophrenic patients, the use of neuroleptics for other conditions requires further evaluation. 13 references.

003761 Avery, Mary Ellen; Chernick, Victor. Children's Hospital Medical Center, Boston, MA 02115 **On decision making surrounding drug therapy: a continuing dilemma.** New England Journal of Medicine. 296(2):102-103, 1977.

In an editorial, the question of when data on the use of specific drugs will be sufficient, who decides, when it is still "experimental" to use certain drugs, and when is it malpractice to withhold them are examined in terms of glucocorticoids which is administered to women threatened with premature delivery in the presence of evidence of fetal lung immaturity . It is noted that the therapeutic conundrum also works in reverse, and the question of when is it appropriate to stop using a therapeutic drug or modality is discussed. A system that responds quickly to each new report of efficacy would endorse some drugs prematurely; a body of experts could come to a popular but misguided conclusion; a federal agency might be too conservative or slow to respond. The weight of informed opinion, through scientific presentation in publication, eventually influences practice. It is hoped that the courts appreciate this necessary state of affairs and allow due time for establishment of accepted practice in drug therapy. 4 references.

003762 Axelsson, Rolf. Department of Psychiatry III, Lillhagen's Hospital, S-42204 Hisings Backa, Sweden **On the serum concentrations and antipsychotic effects of thioridazine, thioridazine side-chain sulfoxide and thioridazine side-chain sulfone, in chronic psychotic patients.** Current Therapeutic Research. 21(4):587-605, 1977.

The antipsychotic effect and side-effects of thioridazine and its main nonconjugated metabolites were compared by assessing the pattern of thioridazine and thioridazine metabolites during treatment with equipotent doses of thioridazine, thioridazine side-chain sulfoxide, and thioridazine side-chain sulfone. The patients experienced more side-effects during treatment with the metabolites than during treatment with thioridazine, and the number of side-effects in each patient varied significantly with the serum concentrations of the side-chain sulfoxide and the side-chain sulfone. A qualitative difference was observed between the clinical effect of the metabolites and of thioridazine. During treatment with the thioridazine metabolites the patients gradually showed signs of depression, apathy and restlessness but not during treatment with thioridazine. This in combination with the increase in the severity and number of side-effects made the two thioridazine metabolites unsuitable as alternative drugs for these patients. 28 references. (Author abstract modified)

003763 Baile, Walter F.; De Paulo, J. Raymond, Jr.; Schmidt, Chester W., Jr. Department of Psychiatry, Johns Hopkins University, School of Medicine, Baltimore, MD 21205 **Emergency room management of organic brain syndromes caused by over the counter hypnotics.** Maryland State Medical Journal. 26(1):61-63, 1977.

Because of the dangers that may occur if physical symptoms are overlooked in the emergency room treatment of patients who have ingested nonprescription sleep medications, three cases of scopolamine induced psychoses and the management problems they posed are reviewed. Nonprescription sleeping products, sold under many trade names are composed primarily of scopolamine and methapyrilene, although a few contain bromide salts. In all three cases described the problem was known to be an overdose of an over the counter sleeping medication. Each patient had several or all of the physical signs associated with scopolamine poisoning. Even so, none received physostigmine, and one patient was committed to a state hospital with a diagnosis of schizophrenia, while the other two patients were also thought to be schizophrenic until the organic brain syndrome was diagnosed by a psychiatric consultation. The diagnosis of scopolamine poisoning was side tracked by bizarre symptoms. It is concluded that mental and physical examinations must be carried out and the possibility of scopolamine ingestion must be kept in mind when diagnosing treatable organic brain syndromes. 11 references.

003764 Beaumont, G. Research and Medical Department, CIBA-GEIGY (UK) Limited, Macclesfield, Cheshire, England **Practical considerations on the use of clomipramine (Anafranil) in general practice: an updated review.** Journal of International Medical Research (Northampton). 5(Supplement 1): 46-50, 1977.

At a symposium held at Rabat, Malta, in November, 1976, an updated review was made of practical considerations to using clomipramine in general practice, and the subject of dosage of clomipramine in depression and phobic and obsessional disorders was discussed. The expectation of success was reported and a recommendation made to adopt flexible dosage. Some side-effects were considered and stress was laid on distinguishing between unwanted pharmacological effects and serious toxic effects. Serious adverse reactions are rare. Contraindications, both relative and absolute, were discussed. The importance of possible drug interactions was emphasized. 27 references. (Journal abstract modified)

003765 Beaumont, G. Research and Medical Department, CIBA-GEIGY (UK) Limited, Macclesfield, England **Sexual side-effects of clomipramine (Anafranil).** Journal of International Medical Research (Northampton). 5(Supplement 1):37-44, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the effects of depressive illness and of clomipramine therapy in doses of 30mg and 75mg daily on sexual appetite and performance was discussed. A special questionnaire was devised to gather information on sexual habits before illness, during illness, and following treatment. It proved difficult to differentiate between the beneficial effects of recovery from depression and the possible adverse drug effects on sexual activity. Two patients dropped out of the study because of supposed sexual side-effects -- a male with ejaculatory difficulties and a female with orgasmic impotence. Fifty four patients completed the sexual questionnaire and a four week course of clomipramine. There were nineteen males and thirty five females. Sixty eight percent of males and 57% of females had their sex life impaired by depressive illness. Coital rate was decreased and depression interfered with performance and satisfaction. Clomipramine therapy seemed to have advantageous and disadvantageous effects. The advantageous effects were probably associated with improvement in depressive illness. There was evidence that clomipramine had an adverse effect sexually in 26% of males and 14% of females. The effect was dose related in females. (Journal abstract)

003766 Benjamin, Fred B. National Highway Traffic Safety Administration, Washington, DC **A review of the safety hazard due to poor health, drugs, and their interaction.** Human Factors. 19(2):127-137, 1977.

A review of statistical and clinical research literature is presented to elucidate the interactions of poor health, drug use, and alcohol consumption on driver performance and safety. Accident involved drivers consist of two separate population groups; those involved in fatal accidents and those involved in nonfatal accidents. One of the principal characteristics of the fatal accident group is the lower accident survival rate and is likely to be improved by the use of therapeutic drugs. In the nonfatal group, impaired driving performance is the most significant hazard. Some of the therapeutic psychoactive drugs, specifically those that depress the central nervous system, tend to impair driving performance. This is likely to lead to daytime, nonfatal accidents. Chronic alcoholism is likely to lead to health impairment and lowered accident survival rate, and acute alcoholism is likely to impair driving performance. 30 references. (Author abstract)

003767 Benowitz, Neal L.; Jones, Reese T. Langley Porter Neuropsychiatric Institute, 401 Parnassus Ave., Room A-309, San Francisco, CA 94143 **Prolonged delta9-tetrahydrocannabinol ingestion: effects of sympathomimetic amines and autonomic blockades.** Clinical Pharmacology and Therapeutics. 21(3):336-342, 1977.

To evaluate the possible effects of delta9-tetrahydrocannabinol (THC) on autonomic nervous system function, cardiovascular responses to intravenous isoproterenol, phenylephrine, atropine, and propranolol were compared in 10 hospitalized volunteers before and after 14 days of THC ingestion. There was no significant alteration in responses to isoproterenol or phenylephrine, although in one subject the pressor effect of phenylephrine was considerably augmented by THC. Heartrates after parasympathetic (atropine) blockade and after combined parasympathetic and sympathetic (propranolol) blockade were significantly greater during THC ingestion. These and other data presented are consistent with the picture of reduced sympathetic and enhanced parasympathetic activity described in animals on THC. During THC ingestion, atropine had a pronounced pressor effect, which might represent a clinically significant drug interaction. 28 references. (Author abstract)

003768 Biggs, John T.; Riesenberg, Robert A.; Ziegler, Vincent E. Washington University School of Medicine, 4940 Audulon Ave., St. Louis, MO 63110 **Overdosing the tricyclic overdose patient.** American Journal of Psychiatry. 134(4):461-462, 1977.

In a letter to the editor of the American Journal of Psychiatry, in reference to two articles on treating the tricyclic overdose patient, some findings contrary to those reported in the articles are discussed. Therapy for the tricyclic overdose patient ought to be limited to the prompt use of respiratory support to avoid hypoxia that may prompt cardiac arrhythmias. Overzealous use of drugs in treating the overdose patient may create additional medical emergencies rather than solve them. A list of five specific disagreements with the treatment of the tricyclic overdose patient as outlined in the two articles is presented. 4 references.

003769 Blumenthal, Ivan; Lindsay, Sheila. Apartment 3Б, 2151 Ridge Avenue, Evanston, IL 60201 **Neonatal barbiturate withdrawal.** Postgraduate Medical Journal (Oxford). 53(617):157-158, 1977.

An infant with neonatal barbiturate withdrawal syndrome is reported. The clinical features, diagnosis, and treatment of this condition are discussed. A retrospective review of 53 infants of barbiturate treated epileptic mothers indicated a high incidence of "jitteriness" (17%) and feeding problems (36%) in the immediate neonatal period. 7 references. (Journal abstract)

003770 Brown, Martha M.; Boosinger, Jeannene K.; Henderson, Melinda; Rife, Sharon Swift; Rustia, Janice Kubat; Taylor, Odessie; Young, W. Wayne. Nursing Care Research Center, College of Nursing, University of Nebraska, Omaha, NE **Drug-drug interactions among residents in homes for the elderly: a pilot study.** Nursing Research. 26(1):47-52, 1977.

An investigation of the epidemiological potential for clinically significant drug/drug interactions, a subclass of adverse drug responses, in two homes for the elderly is described. The agent (drugs), host (residents), and environment (rural and urban nursing homes) were studied. Drug profiles on 188 subjects were compiled and screened by computer. Of these, 100 (80 in the rural home and 20 in the urban home) had the poten-

tial for clinically significant drug/drug interactions. Laboratory diagnostic procedures essential to confirm the unintentional interaction of two or more drugs were beyond the scope of the study; therefore, physicians independently reviewed the records of 66 residents who could be interviewed, agreeing that 27 residents were potential drug/drug interactors. These subjects had twice as many drug products and three times as many pro re nata products prescribed for them as did subjects without the potential for drug/drug interaction. The possible cause of interaction found most frequently was digitalis combined with thiazide or furosemide. The results of this pilot study suggest several implications for practice within the research setting. 37 references. (Author abstract)

003771 Coleman, Mary. Georgetown University School of Medicine, Washington, DC 20008 **Myoclonus in the young after 5-hydroxytryptophan.** New England Journal of Medicine. 296(14):820, 1977.

In a letter to the editor, comments are presented on the appearance of myoclonus in the young following the administration of 5-Hydroxytryptophan (5-HTP). It is reported that 5-HTP was found to initiate myoclonic seizures in 15% of a group of patients receiving long-term 5-HTP therapy. It was also observed that if the infantile spasms syndrome is about to develop in a patient with the trisomy 21 form of Down's syndrome on a spontaneous basis the whole blood 5-HT level rises to the top normal or above normal range in the month before the clinical onset of myoclonic jerks. Further data and their implications are related to the subject. 5 references.

003772 Dysken, Maurice W.; Chan, Carlyle H. University of Chicago, 950 East 59th Street, Chicago, IL 60637 **Diazepam withdrawal psychosis: a case report.** American Journal of Psychiatry. 134(5):573, 1977.

A case report of a patient with a history of alcohol and sedative abuse who developed a withdrawal psychosis following discontinuation of a small amount of maintenance diazepam is reported. A 49-year-old man was admitted to a psychiatric hospital with anxiety, depression, and restlessness. He had been taking diazepam for 7 years for anxiety associated with hyperventilation. When medication was discontinued, he developed psychotic symptoms which disappeared when diazepam was reinstated. It is suggested that maintenance benzodiazepine compounds should not be discontinued abruptly in patients with histories of chronic sedative abuse or alcoholism, regardless of the current maintenance dose. As in other forms of addiction, gradual withdrawal of the drug is indicated. 5 references. (Author abstract modified)

003773 Edis, R. H.; Mastaglia, F. L. University Department of Medicine, Perth Medical Centre, Nedlands, 6009, Australia **Vertical gaze palsy in barbiturate intoxication.** British Medical Journal (London). No. 6054:144, 1977.

The occurrence of a vertical gaze palsy in a patient intoxicated with a medium acting barbiturate is reported. The relatively high level of butobarbitone in the patient's blood and subsequent clearing of the abnormal eye signs within days of withdrawal of barbiturates confirmed their causal role. This case indicates that conjugate vertical gaze palsy may be present as an additional eye sign in the conscious barbiturate intoxicated patient. The recognition of the fact could avoid unnecessary neuroradiological investigation in such patients. 5 references.

003774 Edstrom, A.; Persson, G. Department of Psychiatry, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden **Comparison of side effects with coated lithium carbonate tablets and lithium sulphate preparations giving medium-slow and slow-release. A double-blind cross-over study.** Acta Psychiatrica Scandinavica (Stockholm). 55(2):153-158, 1977.

Side-effects with coated, rapidly dissolving lithium carbonate tablets, medium slow release and slow release lithium sulphate tablets, all administered twice a day, were compared in a double-blind, cross-over study in 27 patients who had only used lithium carbonate tablets. The relation between medication and meals was not standardized. The rapidly dissolving tablets and the medium slow release tablets had a similar tendency to produce side-effects, while slow release tablets more often produced purgative side-effects than the other two preparations did. 12 references. (Journal abstract)

003775 Elizur, Avner; Graff, Eran; Steiner, Meir; Davidson, Shamai. Shalvata Psychiatric Center, Hod Hasharon, Israel **Intra/extra red blood cell lithium and electrolyte distributions as correlates of neurotoxic reactions during lithium therapy.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 55-64).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December, 1975, a study of the distributions of lithium (Li) and other electrolytes in red blood cells (RBC) and plasma during neurotoxic reactions resulting from Li therapy is reported. During Li toxicity, the intracellular/extracellular (RBC/plasma) ratio of Li increased, plasma potassium (K) levels decreased, plasma magnesium (Mg) levels increased, and plasma sodium (Na) and calcium (Ca) levels were unchanged. In the RBC, NA levels increased, K levels decreased, and Mg levels increased during Li toxicity. These findings occurred both in patients receiving Li alone and in patients receiving Li plus a tricyclic antidepressant. It is suggested that the data provide evidence for the importance of the intracellular/extracellular distributions of Li and other electrolytes during Li treatment and that the distributions may have predictive value for Li neurotoxicity. 35 references.

003776 Falk, R. H.; Nisbet, P. A.; Gray, T. J. Brook General Hospital, London SE18 41W, England **Mental distress in patient on disopyramide.** Lancet (London). No. 8016:858-859, 1977.

A case report is presented of a psychotomimetic reaction to the drug disopyramide, prescribed for repetitive parozysmal ventricular tachycardia. Within 24 hours of starting treatment with disopyramide, the patient became agitated and distressed and her mental state got progressively worse over the next 3 days, with delusions of persecution and auditory hallucinations. Disopyramide was withdrawn and she made a complete mental recovery over the next day, with recurrence of multiple ventricular ectopic beats. Disopyramide may cause acute psychosis, and should be used with caution, particularly in unsupervised patients.

003777 Fama, P. G. no address **Datura poisoning.** New Zealand Medical Journal (Dunedin). 85(581):108, 1977.

In a letter to the editor, the cases of four young patients who had ingested a brew of Datura stramonium or thornapple in search of an altered state of consciousness are examined. They subsequently became acutely intoxicated by hyoscine poisoning, the clinical picture of which could be confused with those of amphetamine psychosis, LSD intoxication, or even acute schizophrenia. It is suggested that, in doubtful cases, it

is wise to question both patient and acquaintances about recent experimentation with plant extracts.

003778 Fann, William E. Psychiatry Service, Veterans Administration Hospital, Houston, TX 77031 **Some problems in the treatment of depression with pharmacological agents.** Psychiatry Digest. 38(2):19-23, 1977.

Some of the actions and interactions of pharmacotherapeutic agents which may lead to secondary problems in the treatment of depression are discussed. Psychotropic drug activity is influenced by a variety of biological events which impose many significant variables on the outcome of therapy. Specific ways in which drugs can interact in the gastrointestinal tract, at the hepatic level, at the neuronal level, at the renal level, and at the drug mediator level are detailed. Physiological factors within the gastrointestinal tract are described in relation to drug availability, but once absorbed, may interact with other drugs given concomitantly and with endogenous compounds. Some stimulant and sedative agents alter liver metabolism of the drug, causing changes in the clinical effect. All of the marketed tricyclics and neuroleptics block activity of the presynaptic adrenergic membrane transport system. There is also evidence that tricyclic antidepressants interfere with the hypotensive effect of the centrally active antihypertensive clonidine. Interactions at the renal level may occur in patients treated with lithium and who are given concomitant doses of sodium depleting drugs. It is argued that research into the effects on psychotropic agents of dietary components, endocrinopathy, and other xenobiotics is required if physicians are to have a more rational system of prescription of the useful but problematic drugs they use in practice.

003779 Faux, Eugene J. Outpatient Services, Timpanogos Mental Health Center, Provo, UT **Acute organic brain syndrome with propranolol and methyl-dopa.** In: Thorpe, P., Provo Papers. Provo, UT, Utah State Hospital, 1977. 83 p. (p. 7-12).

A case study is reported in which the combination of propranolol and methyl dopa is thought to have been responsible for a toxic psychosis. Each of these drugs could have serious depleting effects on the sympathetic nervous system. As a decarboxylase inhibitor, methyl dopa blocks the production of dopamine, thus interfering at the formation of serotonin and norepinephrine. Propranolol as a beta-adrenergic receptor blocking agent reduces the sympathetic effect from another flank, not only providing the blockade but also a Quinidine-like action which depresses cardiac function with its anesthetic membrane effect. It seems highly probable that the depletion of these catecholamines were responsible for a toxic psychosis characterized by a catatonic episode with nocturnal visual hallucinations and the confusion described in the patient's history. 3 references.

003780 Fieve, Ronald. Department of Psychiatry, Columbia University, New York, NY **Pharmacotherapy here and abroad: differences in side effects.** Spanish Speaking Mental Health Research Center. Los Angeles, CA, SSMHRC, 1977. 110 p. (p. 93-95).

A panel discussion of differences of pharmacotherapeutic side-effects found in U.S. and Caribbean patients, held during a joint meeting of the Puerto Rican Medical Assn.,the Caribbean Psychiatric Assn.,and the American Psychiatric Assn. in May 1976 in Puerto Rico, is summarized. The actions and side effects of the major and minor tranquilizers, tricyclic antidepressants, MAO inhibitors, lithium carbonate and the hypnotics were systematically examined. It was found that drug actions and side-effects were relatively constant in both cultures, although individual variations were seen. Future intercultural collaboration on pharmacogenetic differences was recommended. Only minor behavioral differences in side-effects such as photosensitivity, weight gain, disclosure of impotence, and intolerance to anticholinergic symptoms in the Caribbean at comparable U.S. doses was discerned. Climate differences affecting lithium metabolism were also discussed. It was suggested that empirical research into psychopharmacological transcultural differences is needed.

003781 Foster, Jeffrey R.; Gershell, William J.; Goldfarb, Alvin I. Mt. Sinai School of Medicine, 111 East 85th Street, NY 10028 **Lithium treatment in the elderly. I. Clinical usage.** Journal of Gerontology. 32(3):299-302, 1977.

Problems associated with use of lithium carbonate to treat manic aspects of bipolar mood disorders in the elderly are reviewed, with case studies, and a special dosage titration method of initiating lithium treatment is discussed. Both therapeutic and toxic side-effects occur at much lower dosage and serum levels of lithium in the elderly than in young persons; incidence of unique drug sensitivity were frequently encountered. Lithium doses under 900mg daily and blood levels under 1.0mEq/liter are recommended, with a target serum range of 0.4to 0.6or 0.7mEq/liter. The need for careful clinical monitoring rather than reliance on lithium blood levels is emphasized. 10 references. (Author abstract modified)

003782 Fras, Ivan; Karlavage, John. Child Psychiatry Unit, Broome County Mental Health Clinic, 3311 E. Main St., Endwell, NY 13760 **The use of methylphenidate and imipramine in Gilles de la Tourette's disease in children.** American Journal of Psychiatry. 134(2):195-197, 1977.

Two case studies are presented in which children with Gilles de la Tourette's disease were treated with methylphenidate or imipramine, and in both cases, these medications exacerbated symptoms. These pharmacologic agents should be used cautiously in treating patients with possible movement disorders (tics). These results are interpreted as lending support to the catecholamine hypothesis of the etiology of Gilles de la Tourette's disease. 8 references. (Author abstract modified)

003783 Gardner, Robert E.; Matus, Simon. O'Berry Center, Goldsboro, NC 27530 **Rickets and anticonvulsants in mentally retarded patients.** North Carolina Medical Journal. 38(2):94, 1977.

In a letter to the editor, results of a study of rickets and anticonvulsants in mentally retarded patients are presented. Results indicated that there is a large percentage of chemical enzyme abnormalities in the group taking anticonvulsants. A small percentage showed evidence of healed rickets on X-ray examination. Patients in the anticonvulsant group all had received anticonvulsants (dilantin, phenobarbital, tegretol, or combination of these drugs) for at least 5 years. 4 references.

003784 Gardos, George. Boston University School of Medicine and Institute for Rehabilitation and Research, Boston State Hospital, Boston, MA 02124 **Dyskinesia after discontinuation of compound analgesic containing oxycodone.** Lancet (London). No. 8014:759-760, 1977.

In a letter to the editor, a case study is reported of an unusual, acute dyskinetic reaction to abrupt cessation of percodan, a compound analgesic containing oxycodone, aspirin, phenacetin, and caffeine. The withdrawal dyskenesia involved severe rocking movements and associated choreoathetoid

movements of the tongue and fingers; the patient responded to treatment with diphenhydramine but not to chlorpromazine. It is not possible to relate specific movement abnormalities to specific neurotransmitter imbalance.

003785 Gerlach, Jes. Sct. Hans Hospital, Dept. E., DK-4000 Roskilde, Denmark **Relationship between tardive dyskinesia, L-dopa-induced hyperkinesia and Parkinsonism.** Psychopharmacology (Berlin). 51(3):259-263, 1977.

The localization and the intensity of tardive dyskinesia and L-dopa induced hyperkinesia in patients with paralysis agitans were compared, the influence of age on L-dopa hyperkinesia and tardive dyskinesia was compared, and L-dopa induced involuntary movements were related to the symptoms, localization, and severity of Parkinson's disease. In 16 psychotic patients with neuroleptic induced tardive dyskinesia and 16 patients with Parkinson's disease and L-dopa induced hyperkinesia it was found that: 1) tardive dyskinesia was localized almost exclusively to the oral region, 2) L-dopa hyperkinesia showed an increasing tendency to oral preponderance with age, and 3) extraoral L-dopa hyperkinesia was related to the localization and severity of pretreatment Parkinsonism, and more to bradykinesia than to rigidity and tremor. It is concluded that the irreversible neurotoxic effect of neuroleptic drugs may be associated with age related changes in the oral somatotopic region of the basal ganglia, and that the pathophysiology of involutary hyperkinesia in neuroleptic treated psychiatric patients and in L-dopa treated Parkinson patients may consist of a primary dopamine deficiency and a secondary relative hyperactivity in the dopaminergic system possible corresponding to hypoactivity in the cholinergic system. 27 references. (Author abstract modified)

003786 Giannini, A. James. no address **Side effects of metronidazole.** American Journal of Psychiatry. 134(3):329-330, 1977.

A case of disorientation and depression during a course of metronidazole (flagyl) therapy is discussed in order to note the side-effects of the drug. The patient was a 19-year-old women who weighed 44.1kg. She was treated for urogenital trichomoniasis with 250mg of orial metronidazole t.i.d. Seven days after the initiation of metronidazole therapy the patient complained of difficulty falling asleep, difficulty concentrating, decreased libido, and estrangement from her boyfriend and family as well as depressive feelings, and loss of appetite. Despite an excellent academic record she had developed fears of failing her courses. She talked slowly during the mental state exam and had depressed facies. She was unable to perform "serial sevens" and had difficulty remembering the date or the name of her family doctor. The metronidazole therapy was suspended and 4 days later she was asymptomatic. Although anorexia and mild depression have been separately described with metronidazole therapy, this is the first known case to involve concomitant disorientation and moderate depression. 1 reference.

003787 Gilbert, Roberta M.; Knight, Martha. 4121 West 83rd Street, Suite 206, Prarie Village, KS 66208 **Patient-drug monitoring: laboratory studies for psychotropic drugs.** Journal of the Kansas Medical Society. 78(1):20-22, 1977.

In order to determine what laboratory studies drug companies recommend for patients receiving their psychotropic drugs on a long-term basis, 16 companies were polled regarding specific tests necessary to monitor possible untoward effects and at what intervals tests should be done. Tables listing recommended studies for 20 different brand name psychotropic pharmaceuticals are presented as well as a listing for drugs for which the companies felt no tests were necessary except when the patient was presenting side-effects. The most frequently suggested tests were periodic blood counts and hepatic and renal studies. In general no clear mandate for monitoring drugs was offered by the companies on the rationale or desirability of ongoing laboratory studies. It is concluded that with the exception of weekly transaminenase and alkaline phosphatase studies in the first 8 weeks of treatment, routine studies on a regular basis are not helpful unless warrented by the patient's clinical condition. Of paramount importance in avoiding serious side-effects of psychotropic drugs is an alert and well informed doctor and patient. 17 references.

003788 Greenblatt, David J.; Allen, Marcia D.; Shader, Richard I. Boston Collaborative Drug Surveillance Program, 400 Totten Pond Rd., Waltham, MA 02154 **Toxicity of high-dose flurazepam in the elderly.** Clinical Pharmacology and Therapeutics. 21(3):355-361, 1977.

To assess the potential hazards of flurazepam (Dalmane) therapy of insomnia in the elderly, the relation of dosage and patient age to the frequency of flurazepam attributed adverse reactions was studied in 2542 hospitalized medical patients. Adverse reactions, predominantly unwanted residual drowsiness, were reported in 78 flurazepam recipients (3.1%). None of the adverse reactions were serious. The frequency of reported toxicity increased with average daily dose, ranging from 1.3% among those receiving less than 15mg/day to 12.3% at doses of 30mg/day or more. Toxicity increased with age, progressively from 1.9% among those under 60 to 7.1% among those 80 or over. Unwanted effects of high dose flurazepam were observed much more commonly in the elderly. Only 2.0% of those 70 years of age or older experienced adverse reactions at doses under 15mg/day, as opposed to 39.0% at 30mg or more per day. Low doses of flurazepam appear to be safe for elderly individuals, but they are susceptible to unwanted central nervous system depression at high doses. 25 references. (Author abstract)

003789 Greenblatt, David J.; Allen, Marcia D.; Noel, Barbara J.; Shader, Richard I. Clinical Pharmacology Unit, Massachusetts General Hospital, Boston, MA 02114 **Acute overdosage with benzodiazepine derivatives.** Clinical Pharmacology and Therapeutics. 21(4):497-514, 1977.

A review of admission to Massachuetts General Hospital for acute overdosage with one or more psychotropic drugs between 1962 and 1975 is presented, and the increase in frequency of benzodiazepine derivate overdosages is much larger than for other psychotropic drugs. Only 12 admissions were due to benzodiazepine overdosage alone, and none of these patients were seriously ill or had significant complications. Multiple drugs were ingested in the other 87 cases, and the frequency and severity of complications among these individuals depended upon the type and quantity of other non-benzodiazepines taken. For example, 21 of 31 patients who ingested benzodiazepines together with barbiturates experienced severe central nervous system (CNS) depression, and 14 of 31 required assisted ventilation. However, the frequency of such complications was nearly identical in a group of patients who ingested barbiturates alone. This report and a review of the literature suggest that serious intoxication following overdosage with a benzodiazepine derivative alone is unusual. Ingestion of benzodiazepines together with other drugs appears to be considerably more common that benzodiazepine overdosage alone as a cause of intoxication. The severity of intoxication in such cases of multiple drug ingestion probably de-

pends largely on the type and quantity of nonbenzodiazepines. 115 references. (Author abstract modified)

003790 Griggs, E. Allen; Ward, Michael. Lake Cumberland Medical Center, Somerset, KY **LSD toxicity: a suspected cause of death.** Journal of the Kentucky Medical Association. 75(4):172-173, 1977.

A suspected cause of death by LSD toxicity is described in which extremely high liver tissue level of lysergic acid diethylamide (LSD) was measured in a 34-year-old male in whom autopsy showed no anatomic cause of death. Using general comparative data, the subject would have seemed to have received an LSD dose equivalent to 23 times the previously calculated lethal human dose of LSD. It is suggested that the subject expired from CSN mediated respiratory arrest due to the direct toxic effect of massive LSD overdose. 10 references.

003791 Gualtieri, C. T. Division of Child Psychiatry, North Carolina Memorial Hospital, Chapel Hill, NC 27514 **Imipramine and children: a review and some speculations about the mechanism of drug action.** Diseases of the Nervous System. 38(5):368-374, 1977.

A review of research literature into the use of imipramine (IMI) in a variety of pediatric situations, with particular emphasis on the pharmacokinetics of IMI in children, is presented. Researches indicate that IMI is a useful drug for a number of pediatric conditions; however, use is not without risk, ought to be reserved for those cases in which other, more conventional therapies have proven ineffective. IMI may be of particular benefit for children who are enuretic, hyperactive, or school phobic. Preliminary reports hint at its usefulness in pavor nocturnus and somanambulism, depressive states, petit mal epilepsy, encopresis, head banging, some alleric conditions and certain types of psychosis. In contrast to adults, IMI has a rapid onset of action in children who respond. This may have to do with pharmacokinetic differences in protein binding and fat distribution. In some children, tolerance to the drug's beneficial effects may develop in 8 to 12 weeks. IMI is known to potentiate NE systems by inhibiting presynatpic reuptake. However, the drug possesses a wide range of biologic activity, and there is reason to believe that, in children as well as adults, its effectiveness may have to do with influences on several neurochemical systems; perhaps by regulating adrenergic/cholinergic balance, or by influencing serotnonigergic transmission. Further research into the clinical usefulness of IMI in children and its neurochemical and pharmacokinetic mechanisms is suggested. 110 references. (Author abstract)

003792 Haddad, Rolando I. no address **Blue skin pigmentation and chlorpromazine.** Journal of the Kentucky Medical Association. 75(3):124-126, 1977.

A case report of a 51-year-old male paranoid schizophrenic who developed blue skin pigmentation as a result of chlorpromazine therapy is presented and previous reports of this reaction to the drug are reviewed. The patient who had been on long-term chlorpromazine dosages during psychiatric hospitalization, developed extreme dark blue pigmentation of the face and hands after exposure to sunlight. At that time thioridazine and trifluoperazine were substituted for the chlorpromazine. Skin pigmentation was still evident after a 5 year time lapse since the discontinuance of chlorpromazine therapy. The first report of abnormal skin pigmentation associated with chlorpromazine was published in 1957. Previous reports of unusual pigmentation of the eyes and skin associated with phenothiazines indicates a higher incidence of this reaction in White females living in northern latitudes. Tardive dyskinesia has been mentioned in association with phenothiazine accumulation on the melanosomes in the pigmented nerve cell of substantia nigra and locus coeruleus. Reported incidence of this complication with phenothiazines has been 1% or less. 14 references.

003793 Himmelhoch, Jonathan M.; Forrest, John; Neil, John F.; Detre, Thomas P. Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara St., Pittsburgh, PA 15261 **Thiazide-lithium synergy in refractory mood swings.** American Journal of Psychiatry. 134(2):149-152, 1977.

The dangers inherent in the use of lithium salts in combination with thiazide diuretics are recounted, and detailed clinical/pharmacologic data on 13 patients which suggest that thiazides are useful in the treatment of lithium induced nephrogenic diabetes insipidus is presented. It is theorized that thiazides actually synergize with lithium to produce improved mood control in some lithium refractory manic-depressive patients. The unfortunate experience with lithium chloride as a salt substitute in the 1940's is discussed, and is seen as still directing the clinical usage of lithium carbonate. Although physicians are warned that lithium salts should never be used in low sodium situations, it has been shown that thiazide diuretics may be safely used in the treatment of lithium induced nephrogenic diabetes insipidus. 29 references. (Author abstract modified)

003794 Hoenig, J.; Chaulk, R. Memorial University of Newfoundland, St John's, Newfoundland **Delirium associated with lithium therapy and electroconvulsive therapy.** Canadian Medical Association Journal (Ottawa). 116(8):837-838, 1977.

In a letter to the editor, the case report of a 32-year-old male who developed delirium following electroconvulsive therapy (ECT) and lithium therapy is presented. The patient initially presented with acute manic phases, subsequently with subdelirium, severe confusion and visual agnosia. Diagnosis was severe encephalopathy with acute organic psychosyndrome. The patient's condition returned to normal following withdrawal of lithium and administration of haloperidol and benztropine mesylate. Despite serum lithium concentrations well below the toxic range, encephalopathy appears to have been precipitated by the combination of lithium and ECT. It is suggested that if ECT is administered to a patient receiving lithium, the serum concentration should first be reduced to very low values. 6 references.

003795 Hyams, Stanley W.; Keroub, Claudette. Department of Ophthalmology, Central Emek Hospital, Afula, Israel **Glaucoma due to diazepam.** American Journal of Psychiatry. 134(4):447-448, 1977.

A case report is presented of an epileptic patient who developed severe angle closure glaucoma, after 3 years of daily medication with 20mg diazepam. The patient had also received 300mg diphenylhydantoin and 200mg phenobarbital daily for 15 years. It is noted that this is the first case of glaucoma encountered in patients taking diazepam. Definite causal relationships have been demonstrated only with atropine and trihexphenidyl hydrochloride. It is suggested that patients over 40 years of age be examined by an ophthalmologist before starting long-term therapy with anticholinergic drugs, no matter how minor this drug action may be. 7 references.

003796 Jaffe, Charles M. Inst. for Psychosomatic and Psychiatric Research and Training, 2959 S. Cottage Grove Ave., Chicago, IL 60616 **First-degree atrioventricular block**

during lithium carbonate treatment. American Journal of Psychiatry. 134(1):88,89, 1977.

The case of a patient with first degree atrioventricular (AV) block that was robably induced by lithium carbonate and that returned to normal when the drug was withdrawn is presented. The patient was a 21-year-old woman who was admitted to the hospital during an acute manic episode characterized by pressured speech, flight of ideas, grandiose and paranoid ideation , and marked increase in energy. Lithium carbonate treatment was begun on the tenth day of hospitalization. Electrocardiogram (ECG) studies conducted from 21 to 23 days following initiation of lithium treatment revealed a first degree AV block which stabilized after lowering of the dose and subsequent withdrawal. The need for frequent ECG monitoring of patients treated with lithium is emphasized, and other cardiac side-effects attributed to this drug are discussed. 8 references.

003797 Jefferson, James W. Department of Psychiatry, University of Wisconsin, Madison Medical School, Madison, WI 53706 **Psychotropic drug-induced bladder decompensation.** American Journal of Psychiatry. 134(4):451-452, 1977.

A case study of a patient with psychotropic drug induced bladder decompensation is presented, and used to illustrate that prolonged use of multiple drugs may be not only therapeutically unnecessary but detrimental, and that physicians must be able to see beyond the boundaries of their own specialty if comprehensive patient care is to be provided. The subject, a 35-year-old woman, had been receiving a combination of drugs daily for over 7 years which included thioridizine, haloperidol, imipramine, trihexyphenidyl, diphenhydramine, diazepam, and flurazepam. It is imperative that psychiatrists regularly question their patients regarding side-effects; it should not be assumed that the patient will make the association. In addition, as is specifically illustrated in this case, it is important to reassess frequently a patient's need for medication, always seeking the lowest dose and fewest number of drugs to produce the desired effect. Too many drugs and unnecessarily high dosages are common errors in maintenance psychotropic drug therapy. 10 references.

003798 Jellinek, Theodore. North Central Massachusetts Mental Health Ctr., Nichols Road, Fitchburg, MA 01437 **Mood elevating effect of trihexyphenidyl and biperiden in individuals taking antipsychotic medication.** Diseases of the Nervous System. 38(5):353-355, 1977.

To call attention to mood elevation as a side-effect of biperidan HCl and trihexyphenidyl HCl, two anticholinergic antiparkisonian agents, brief case histories of eight schizophrenic patients receiving one or more antipsychotic medications are presented. This is of significance because of the despondency and anergy often seen in schizophrenics taking antipsychotic medication and because of the difficulty discerning the origin of affective changes in the face of polypharmacy. 11 references. (Author abstract)

003799 Jick, Hershel. Boston Collaborative Drug Surveillance Program, 400 Totten Pond Rd., Waltham, MA 02154 **The discovery of drug-induced illness.** New England Journal of Medicine. 296(9):481-485, 1977.

A nonexperimental research strategy and areas of research related to the identification and management of drug induced illness, a problem which will increase as drug use increases, is discussed. For established marketed drugs, research needs depend on the magnitudes of risk of an illness from a drug and the baseline risk. With the drug risk high and the baseline risk low, the problem surfaces in premarketing studies or through the epidemic that develops after marketing. If the drug adds slightly to a high baseline risk, the effect is undetectable. When both risks are low, adverse effects can be discovered by chance, but systematic case referent studies can speed discovery. If both risks are high, clinical trials and nonexperimental studies may be used. With both risks intermediate, systematic evaluations, especially case referent studies, are needed. Newly marketed drugs should be routinely evaluated through compulsory registration and followup study of the earliest users. 31 references. (Author abstract)

003800 Karch, Fred E.; Lasagna, Louis. Department of Pharmacology and Toxicology, University of Rochester Medical School, Rochester, NY 14642 **Toward the operational identification of adverse drug reactions.** Clinical Pharmacology and Therapeutics. 21(3):247-254, 1977.

A decision table algorithm approach toward the development of an operational system for the identification of adverse drug reactions is presented. The algorithm consists of a set of three decision tables designed to be applicable to a wide variety of clinical circumstances. The three tables identify potential drug reactions, assess the certainty of the link between the event and the agent, and evaluate the underlying causes of the identified untoward events. The accuracy of the decision table analysis was evaluated by comparing the algorithm results with the assessments of a group of clinical pharmacologists in 60 cases. On the whole, the performance of the decision table algorithm was considered very good: the algorithm evaluations agreed with the consensus of the clinical pharmacologists on 45 evaluations (71%) and disagreed on 18 (29%). It is pointed out that the procedure for the evaluation of drug reactions is not strictly an operational one: the assessment sequence presented in the algorithm still requires certain important judgments to be made by the operator. The intent was not to achieve 100% accuracy but to provide a framework for systemically evaluating potential adverse drug reactions and reducing the ambiguity that presently characterizes the assessment of adverse drug reactions. 9 references. (Author abstract modified)

003801 Klaiber, Edward L.; Broverman, Donald M.; Vogel, William; Russfield, Agnes; Pokoly, Thomas. no address **Dose levels of estrogen administration and incidence of endometrial hyperplasia. (Unpublished paper).** Rockville, MD, NIMH, 1977. 16 p.

The incidence of endometrial hyperplasia was examined in the endometrial aspirations of 112 premenopausal and postmenopausal women who were being treated cyclically with widely varying dose levels of oral conjugated estrogens (1.25mg to 25mg per day) with a progestin added the last 5 days of estrogen treatment. The high doses of estrogen were being used as an experimental therapy for depression. The incidence of endometrial hyperplasia was related to an interaction of age and estrogen dosage. A 14.8% incidence of endometrial hyperplasia in women under 40 years of age was not related to estrogen dose levels. Women over 40 years old had a 29.4% incidence of endometrial hyperplasia which was related to estrogen dose level. All of the hyperplasias in the older women occurred in those who received 10mg or less per day. No hyperplasia occurred in those receiving more than 10mg per day. These findings are discussed in terms of estrogen and progesterone influence on endometrial shedding and hyperplasia. 18 references. (Author abstract)

003802 Lippmann, Steven; Moskovitz, Richard; O'Tuama, Lorcan. Dept. of Psychiatry, Univ. of Louisville School of Medicine, Louisville General Hospital, 323 E. Chestnut St., Louisville, KY 40202 **Tricyclic-induced myoclonus.** American Journal of Psychiatry. 134(1): 90-91, 1977.

A case of myoclonus induced by amitriptyline, a tricyclic antidepressant, in a 25-year-old female suffering from depression is reported. The patient was treated with 75mg/day of amitriptyline which was increased, by the end of 2 weeks, to 150mg q.h.s. From 3 to 5 days after this dose level was attained, the patient began to experience intermittent single twitching movements of her hand and body. A single night's dose was omitted, and the myoclonus was gone by the following morning. Amitriptyline was reinstated at a dose of 100mg q.h.s. and was maintained at that level for 10 days with no recurrence of symptoms. A second attempt to raise the dose brought back the twitching within 72 hours and a second reduction abolished it. Subsequent attempts to raise the dose to 125mg produced violent jerking. Previous reports of tricyclic induced myoclonus are described, and it is suggested that this side-effect may be caused by a drug induced neurotransmitter imbalance with a relative excess of serotonin over acetylcholine in the basal ganglia as the physiological basis. 8 references.

003803 Majumdar, Sisir K.; Comaish, J. S. Elmdene Alcoholic Treatment Unit, Bexley Hospital, Bexley, Kent, England **Allergy to diazepam.** British Medical Journal (London). No. 6058:444, 1977.

In two separate letters to the editor two cases of allergy to diazepam are discussed and given two different interpretations. In the first letter, reference is made to a patient with a history of being allergic to drugs including chlordiazepoxide and chlorazepate. Since these two drugs are members of the benzodiazepine family to which diazepam also belongs, the patient's allergy seems to be the result of a cross allergenicity between different members of the benzodiazepine group. As the patient had taken chlordiazepoxide and chlorazepate earlier in her life, tissue fixed antibody to the common antigenic moiety (desmethyldiazepam) was already present in the body; this would have led to the reported and very rare anaphylactic reaction (type I immune reaction) in this patient. In the second letter, mention is made of another case of allergy to diazepam. In this case no previous allergy was reported but patch testing with the injectable form of diazepam was positive on two separate occasions. This case seems to leave little doubt and is explained as an example of an epidermal (eczematous) reaction to a systemically administered drug. 2 references.

003804 Matuk, Fairuz; Kalyanaraman, Krishna. Dept. of Neurology, School of Medicine, SUNY at Buffalo, Buffalo, NY **Syndrome of inappropriate secretion of antidiuretic hormone in patients treated with psychotherapeutic drugs.** Archives of Neurology. 34(6):374-375, 1977.

Two cases of inappropriate secretion of antidiuretic hormone (SIADH) during psychotropic drug therapy are reported. In one, the syndrome occurred after administration of a phenothiazine and in the other, a butyrophenone. Both the patients were diagnostically studied for evidence of other disorders, either neurologic or systemic, which could cause this syndrome, with negative results. They responded to fluid and free water restriction with remarkable recovery and no sequelae. It is stressed that psychotherapeutic drug administration must be considered as one of the iatrogenic causes of SIADH. 4 references. (Author abstract modified)

003805 McNamee, H. Brian. Ravenscraig Hospital, Greenock PA16 9HY, England **Drug-dependence clinics.** Lancet (London). No. 8010:541-542, 1977.

In a letter written in response to an editorial, the author agrees that Great Britain's special drug treatment clinics constitute an advance in the management of narcotic addiction. However, two disadvantages of maintaining patients on narcotics for prolonged periods, i.e. that chronic narcotic administration leads to more dysphoric mood states, increased psychopathology, motor retardation, and social isolation and that narcotic maintenance in males is associated with significantly depressed plasma testosterone levels, are pointed out. 2 references.

003806 McNulty, H.; Moorhouse, R. A. South Western Regional Drug Information Service, Bristol Royal Infirmary, Bristol, England **Guide to drug interactions.** Lancet (London). No. 8002:95, 1977.

In a letter to the editor, corrections are suggested in the design, classification system, and information content of the pocket "Medisc." It is mentioned that the small number of drugs on the inner disc means that some well documented interactions, such as levodopa and pyridoxine, cannot be matched. Also, the classification system is said not to differentiate between pharmacological and toxic effects, and does not indicate whether alteration of dosage will correct the effect of the interaction or whether concurrent use of the drugs should be avoided. It is suggested, that to be of value, the disc should be brought up to date regularly, and the device should state that the interaction list is not comprehensive. 1 reference.

003807 Miller, P.; Luscombe, D. K.; Jones, R. B.; Seldrup, J.; Beaumont, G.; John, V. no address **Relationships between clinical response, plasma levels and side-effects of clomipramine (Anafranil) in general practitioner trials.** Journal of International Medical Research (Northampton). 5(Supplement 1): 108-118, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the relationships between clinical response, plasma levels and side-effects of clomipramine were studied in general practitioner trials with depressed patients treated with four different dosage regimes of clomipramine. Seventy patients were originally admitted to the study but blood sampling from one patient was unsatisfactory. Of the 69 acceptable patients, 21 dropped out of the study, 13 because of intolerable side-effects. Of the 49 patients who completed the study a further 17 were rejected from the steady state section of the study because strict sampling criteria were not adhered to, because initial samples were suspect or the dosage was changed during the study. Of the 32 patients considered satisfactory, 9 received clomipramine in a dose of 10mg three times a day, 9 received 30mg in a single dose at night, 9 received 25mg three times a day, and 5 received 75mg in a single dose at night. Steady state of unchanged drug and metabolite was reached after the first week of the four week trial. Each dose appeared to produce a plasma level at which there was a therapeutic response. There was no statistically significant difference between mean drug levels but there was a strong indication that metabolite levels vary with dose. No correlation could be found between clinical response and plasma level of drug or metabolite, although there was a tendency for poor responders to have higher than average plasma levels. There was a poor but positive correlation between plasma levels and side-effects. 1 reference. (Journal abstract modified)

003808 Milner, Louis. Department of Anaesthesia, Centrallasarettet, S-351 85 Vaxjo, Sweden **Allergy to diazepam.** British Medical Journal (London). No. 6054:144, 1977.

A case study of a young woman who suffered an allergic reaction to diazepam is reported. Within two minutes of intramuscular injection she lost consciousness, and her normal vital signs returned only after receiving cortisone and ephedrine injections. This case is considered important because hypersensitivity reactions to the benzodiazepine derivatives have not been reported, although the drugs are known to be tissue irritants as well as having histamine releasing properties.

003809 Moore, N. C. Princess Alexandra's Royal Air Force Hospital, Wroughton, Swindon, SN4 OQJ Wilts, England **Medazepam and the driving ability of anxious patients.** Psychopharmacology (Berlin). 52(1):103-106, 1977.

Anxious adult males (N=14) were administered 16.5mg of medazepam daily in a double-blind crossover design to investigate the effects of the drug on driving ability. The active drug was no more effective than placebo in relieving anxiety, which was rated both clinically and by the Middlesex health questionnaire (MHQ). This may have been because the dose was relatively low for chronically anxious hospital patients. Even this dosage caused significantly higher scores on the MHQ scale for depression. Braking and driving simulator tests were not adversely affected by medazepam. In real driving conditions those taking the drug made significantly more technical, but not dangerous, errors. Pulse and blood pressure were not affected. 12 references. (Author abstract modified)

003810 Mullick, Florabel G.; McAllister, Hugh A. Armed Forces Institute of Pathology, 14th St. NW at Alaska Ave., Washington, DC 20306 **Myocarditis associated with methyldopa therapy.** Journal of the American Medical Association. 237(16):1699-1701, 1977.

Five cases of patients who died suddenly and unexpectedly with myocarditis circumstantially associated with methyldopa are reported. Three were treated with methyldopa and hydrochlorothiazide, two with methyldopa alone. Their ages ranged from 30 to 71 years. In all instances death occurred suddenly, and myocarditis was not suspected clinically. The inflammatory changes in the hearts of these patients were most consistent with a hypersensitivity reaction. Additionally, there was hepatitis consistent with hypersensitivity in four of the cases. It is suggested that clinicians and pathologists should be aware of the possibility of a causal relationship between methyldopa and myocarditis, and should monitor patients carefully. 7 references. (Author abstract modified)

003811 Munoz, Rodrigo A. no address **/Treatment of tricyclic overdose patients./** Dr. Munoz and Drs. Holinger and Klawans reply. American Journal of Psychiatry. 134(4):462, 1977.

In a letter to the editor of the American Journal of Psychiatry, in reference to criticism of a paper on treatment of tricyclic overdose patients, the three specific criticisms considered are discussed: 1) the induction of emesis with ipecac; 2) the casual use of physostigmine; and 3) the use of physostigmine as a diagnostic tool. It is pointed out that the original paper outlined 11 supportive and symptom specific measures for emergency treatment of intoxication with tricyclic antidepressants, and that no criticism of 9 of the measures was presented in the critique. 7 references.

003812 no author. no address **Dangers of dextropropoxyphene.** British Medical Journal. No.6062:668, 1977.

The dangers of using dextropropoxyphene as a common analgesic drug are reviewed with emphasis on drug dependency and self-poisoning. While drug dependency with this compound was considered unlikely, recent reports of addiction and withdrawal symptoms, particularly in the United States, have appeared. Because of the ready availability of the drug and its common usage, poisoning is increasing. The potential effects of the drug for systematic poisoning are greatly increased when it is taken in combination with alcohol. Despite the popularity of the drug, there does not appear to be a substantial advantage in its use over other available analgesics. Because of the hazards inherent in the use of dextropropoxyphene, it is suggested that the prescribing physician carefully justify his choice for this medication. 14 references.

003813 O'Brien, J. Patrick. Private Psychiatric Consultation Service, Warren 1111, Massachusetts General Hospital, 1 Fruit St., Boston, MA 02114 **A study of low-dose amitriptyline overdoses.** American Journal of Psychiatry. 134(1):66-68, 1977.

The safety of the accepted guideline in prescribing amitriptyline which maintains that no more than 1000 to 1200mg of any tricyclic antidepressant should be dispensed to a potentially suicidal patient at one time was tested in light of preliminary findings on the toxicty of low doses of amitriptyline. A total of 20 instances involving 19 individuals who were hospitalized for amitriptyline overdoses was investigated. Findings indicate that 6 of 12 cases of low dose amitriptyline overdoses at levels of 500 to 1000mg were life threatening . Loss of consciousness, coma, and electrocardiogram (ECG) changes were among the symptoms noted. It is concluded that prescription guidelines for tricyclic antidepressants should be tightened and that physicians should prescribe less than a 1 week supply to potentially suicidal patients. 11 references. (Author abstract modified)

003814 Padfield, Adrian; Watkins, John. Dept. of Anaesthetics and Immunology, Hallamshire Hospital Medical School, Sheffield, England **Allergy to diazepam.** British Medical Journal. No. 6060:575-576, 1977.

Possible mechanisms involved in reactions to intravenous (IV) diazepam are reported in a letter to the editor. In five of seven patients treated with diazepam or diazepam diluted with Cremophor EL, alterations in white blood cells suggestive of drug recognition or immunological memory occurred. It is suggested that although Cremophor is unlikely to initiate immunological reactions, its surfactant properties may effectively enable it to act as an adjuvant. It is suggested that the increasingly widespread use of drugs such as diazepam and the tendency to use Cremophor to prevent thrombophlebitis and injection pain during iv administration increases the chances for potential hypersensitivity and may result in an increasing number of reports of anaphylactoid phenomena in the future from drugs considered "safe." 2 references.

003815 Persson, G. Department of Psychiatry, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden **Lithium side effects in relation to dose and to levels and gradients of lithium in plasma.** Acta Psychiatrica Scandinavica. 55(3):208-213, 1977.

The relation between lithium dose, lithium concentrations, and lithium gradients in plasma and the side-effects tremor, nausea, abdominal pains, and loose bowels was studied in 19 subjects. Rapidly dissolving lithium carbonate tablets were used. Tremor was related to higher doses, to higher concentrations, and to higher gradients of lithium in plasma. Nausea was related to higher gradients. Abdominal pain and loose bowels showed no relation to doses, levels or gradients. Concentra-

tions of lithium were dose dependent, while gradients were relatively independent of dose. 13 references. (Author abstract)

003816 Pfefferbaum, Adolf; Berger, Philip A. Veterans Administration Hospital, Palo Alto, CA 94304 **Narcolepsy, paranoid psychosis, and tardive dyskinesia: a pharmacological dilemma.** Journal of Nervous and Mental Disease. 164(4):293-297, 1977.

The case history of a 54-year-old man with concomitant narcolepsy, paranoid psychosis, and tardive dyskinesia is presented and discussed. It is assumed that these disorders may all result from alteration in catecholamines, serotonin, and/or acetylcholine in the central nervous system. The interactions of the various psychopharmacological agents usually used to treat the disorders when they occur separately are considered in terms of current neurotransmitter hypotheses. It is concluded that the management of this case creates a pharmacological dilemma since the agents used for treatment of each of the disorders separately exacerbated one or both of the other two syndromes. 25 references. (Journal abstract modified)

003817 Preskorn, Sheldon H.; Denner, Lee J. Department of Psychiatry, Washington University Medical Center, St. Louis, MO 63110 **Benzodiazepines and withdrawal psychosis: report of three cases.** Journal of the American Medical Association. 237(1):36-38, 1977.

In view of the widespread prescription of benzodiazepines in the United States, three cases of acute psychotic illness following sudden withdrawal from high daily doses of diazepam by patients with no previous history of psychotic illness are described. Presenting symptoms included disorientation, agitation, confusion, hallucination, delusions, and recent memory deficits, lasting 24 hours for two of the patients and 72 hours for the third. Patients were treated with either pentobarbital or diazepam, and slow withdrawal from diazepam was undertaken with no further relapses. One year followup studies indicated no psychotic relapses. It is suggested that gradual withdrewal of benzodiazepines should reduce the possibility of withdrewal psychosis. 10 references. (Author abstract modified)

003818 Quitkin, Frederic; Rifkin, Arthur; Gochfeld, Linda; Klein, Donald F. Affective Disease Clinic, Long Island Jewish-Hillside Medical Center, Hillside Division, P.O. Box 38, Glen Oaks, NY 11004 **Tardive dyskinesia: are first signs reversible?** American Journal of Psychiatry. 134(1):84-87, 1977.

To determine whether tardive dyskinesia is irreversible, 12 psychiatric patients classified as schizophrenic or as suffering from affective disorders and with symptoms of tardive dyskinesia as a result of antipsychotic medication were followed from the inception of the syndrome. Results reveal that first symptoms rarely persisted if antipsychotics were discontinued. It is concluded that the length of time symptoms have persisted prior to drug discontinuation, not age at onset, may be the major variable determining reversibility of the syndrome. 20 references. (Author abstract)

003819 Rainey, John M., Jr. Wayne State University School of Medicine, Detroit, MI 48201 **Disulfiram toxicity and carbon disulfide poisoning.** American Journal of Psychiatry. 134(4):371-378, 1977.

The neurotoxic effects of disulfiram (Antabuse) were compared with those of carbon disulfide, a disulfram metabolite. The results suggest that carbon disulfide is responsible for the behavioral and neurological side-effects of disulfiram. If this is so, then some other toxic effects of carbon disulfide, including parkinsonism, choreoathetosis, and thalamic syndrome may follow the ingestion of more than 5g of disulfiram by adults, and individuals receiving as little as 125mg of disulfiram per day may be at a three to fourfold greater risk for arteriosclerotic cardiovascular disease than a comparable population not receiving the drug. 34 references. (Author abstract)

003820 Reimherr, Fred W.; Hodges, Michael R.; Hill, Gary E.; Wong, K. C. University of Utah Medical Center, Salt Lake City, UT 84132 **Prolongation of muscle relaxant effects by lithium carbonate.** American Journal of Psychiatry. 134(2):205-206, 1977.

The effect of lithium carbonate on prolonging the effect of muscle relaxant drugs was investigated in nine dogs. Inhibition of acetylcholine release and/or synthesis at the neuromuscular junction by lithium would prolong the effect and degree of block seen with neuromuscular blocking agents and would explain the clinical observations and laboratory data. This study suggests that neuromuscular blocking agents should be used with caution in patients who are receiving long-term oral lithium therapy. Since the use of lithium is increasing rapidly in psychiatric practice, psychiatrists should be aware that its interaction with muscle relaxants given for surgical or therapeutic procedures may result in an abnormally prolonged effect. 9 references.

003821 Ribordy, Sheila C.; Denney, Douglas R. Department of Psychology, University of Kansas, Lawrence, KS 66045 **The behavioral treatment of insomnia: an alternative to drug therapy.** Behaviour Research and Therapy (Oxford). 15(1):39-50, 1977.

Treatment of insomnia with drug therapy is criticized and behavioral therapies are seen as preferable. The use of hypnotic drugs to treat insomnia is criticized because of: 1) tolerance effects; 2) carryover effects; 3) alterations in sleep patterns; 4) rebound effects; and 5) attributional effects. Behavioral treatments represent a more viable alternative and are reviewed under four headings: systematic desensitization; applied relaxation; attribution based therapies; and classical conditioning therapies. The behavioral therapies are predicated upon three views of insomnia: first, that insomnia results from excessively high levels of arousal prior to and during sleep; second, that insomnia occurs when the sleep environment lacks sufficient stimulus control over sleeping; and finally, that insomnia is often enhanced and maintained by exacerbation cycles in which worries about not falling asleep interfere even further with one's sleep. 41 references. (Author abstract)

003822 Rifkin, Stephen I. Medical Service (111F), Veterans Administration Hospital, 13000 N. 30th St., Tampa, FL 33612 **Amphetamine-induced angiitis leading to renal failure.** Southern Medical Journal. 70(1):108-109, 1977.

A case history is reported of a 19-year-old woman who presented with manifestations of amphetamine induced angiitis. Her symptoms spontaneously abated, only to recur dramatically with renewed amphetamine usage. Followed up over a 2 year period, she developed malignant hypertension refractory to drug therapy and, subsequently, terminal renal failure. Various etiologic possibilities are discussed, and it is suggested that amphetamine induced angiitis is a distinct clinical entity that is potentially lethal. 8 references. (Author abstract modified)

003823 Sandifer, Myron G. Department of Psychiatry and Family Practice, University of Kentucky Medical Center, Lexington, KY 40506 **Lithium and diuretics.** Journal of the Kentucky Medical Association. 75(3):119-120, 1977.

Potential hazards of combining lithium and diuretics, the mechanisms of interaction, and the treatment of lithium toxicity are discussed, and management of the hypertensive manic or depressive patient is outlined. While lithium alone at normal dosages has few side-effects, the combination of lithium with thiazides may result in nausea, vomiting, diarrhea followed by ataxia, slurred speech and confusion. This toxicity is the result of the effect of thiazides on lithium clearance, which is attributable to a postulated increase in sodium depletion and a compensatory increase in both sodium and lithium reabsorption in the proximal tubule which may double serum lithium levels in a period of one or two weeks. Osmotic diuresis, alkalinization of the urine and administration of aminophylline are indicated for lithium toxicity. Dialysis may be indicated in the most severe cases. Alternatives for the treatment of the hypertensive manic-depressive include the substitution of propanolol in the treatment of the hypertension, or a 50% reduction in lithium dosage prior to treatment with a thiazide. 8 references.

003824 Schaefer, Carl F.; Gunn, C. G.; Dubowski, Kurt M. Department of Anesthesiology, University of Oklahoma Health Sciences Center, P. O. Box 26901, Oklahoma City, OK 73190 **Dose-related heart-rate, perceptual, and decisional changes in man following marihuana smoking.** Perceptual and Motor Skills. 44(1):3-16, 1977.

To determine dose related heartrate, perceptual, and decision-making changes in man following marihuana smoking, information processing was tested in 12 males after smoking marihuana containing 0, 10, or 20mg. of delta9-tetrahydrocannabinol (THC) in three consecutive experimental sessions according to a Latin square protocol. Successful dose control was indicated both by the dose related linear increase observed in heartrate and by preliminary assays of THC metabolites excreted in the urine. During tachistoscopic presentation of varying numbers of circles, statistically significant decrements in information processing occurred as a function of THC dosage. However, adding irrelevant information (triangles) to the display of circles eliminated effects of marihuana on accuracy of counting. Complex reaction times for oddity discrimination increased significantly only after the high dose. Nonetheless, both the social and high doses inappropriately inhibited the general tendency to respond to changing stimuli during oddity discrimination. Marihuana had no effect on field dependence as measured by the Rod-and-Frame test. 25 references. (Author abstract)

003825 Senn, Hans-Jorg; Jungi, Walter Felix; Kunz, Helmut; Poldinger, Walter. Division of Hematology-Oncology, Medical Clinic C, Kantonsspital, CH-9007 Wil St. Gallen, Switzerland **Clozapine and agranulocytosis.** Lancet (London). No. 8010:547, 1977.

In a letter to the editor, two cases of severe agranulocytosis in schizophrenic patients receiving clozapine are reported. One patient died of septic shock. Although the risk of agranulocytosis for clozapine had been assessed as being no greater than the established risk for phenothiazines, it is recommended that: 1) physicians restrict the indications for prescribing clozapine; 2) weekly leucocyte counts should be performed during the first few months of treatment; and 3) patients receiving clozapine must be carefully watched so that the drug can be withdrawn at the earliest onset of leucopenia or signs of infection. 3 references.

003826 Simon, Roger P. no address **Delayed forced down gaze during oculovestibular testing in sedative drug-induced coma.** Neurology. 27(4):346-347, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, delayed forced down gaze during oculovestibular testing in sedative drug induced coma was reported. In 30 patients in coma due to sedative drug intoxication, the tympanic membrane was irrigated for 20 seconds with 50ml of ice water and the oculovestibular responses were observed. Two patients had no response. In two, there was abduction of the ipsilateral eye only, and in two others adduction of contralateral eye only. The most frequent response (22 of 30) was abduction of the ipsilateral eye, with delayed abduction of the contralateral eye. The most striking feature was that in 24 of 30 patients the induced horizontal eye movements were followed, after a 5 to 15 second delay, by marked downward gaze of one or both eyes, persisting for several minutes. All patients had normal eye movements upon recovery. This phenomenon did not occur in 15 patients who were comatose from nondrug related structural or metabolic causes. Therefore, in the comatose patient, delayed forced downward gaze should suggest a diagnosis of sedative drug overdose. (Author abstract modified)

003827 Smith, Harold H., Jr.; Smith, Lili Sikorski. Veterans Administration Center, Bay Pines, FL **WAIS functioning of cirrhotic and non-cirrhotic alcoholics.** Journal of Clinical Psychology. 33(1)(Supplement):309-313, 1977.

A study was done to determine whether the cognitive dysfunction often found in chronic alcoholics would be greater for alcoholics with Laennec's cirrhosis than for alcoholics without cirrhosis. It was hypothesized that cirrhotic alcoholics would score lower than noncirrhotic alcoholics, who in turn would score lower than nonalcoholic, noncirrhotic controls on 1) WAIS Verbal, Performance, and Full Scale IQ; 2) scaled score configuration; and 3) the Wechsler Deterioration Quotient. The WAIS was administered in a Veterans Administration Center to 60 Caucasian male patients aged 35 to 64 who had been assigned to one of the three groups. No differences were found among groups on age, education, or the Information and Vocabulary subtests. Significant differences were found on Verbal, Performance, and Full Scale IQ, the remaining nine subtests, and the Deterioration Quotient. A stepwise discriminate function analysis substantiated these differences. It was concluded that Laennec's cirrhosis is a physical condition that negatively affects intellectual functioning in alcoholics. 21 references. (Author abstract)

003828 Solomon, Kenneth. Dept. of Psychiatry, Albany Medical College, 47 New Scotland Ave., Albany, NY 12208 **Phenothiazine-induced bulbar palsy-like syndrome and sudden death.** American Journal of Psychiatry. 134(3):308-311, 1977.

A case of a phenothiazine/induced bulbar palsy/like syndrome in a patient receiving fluphenazine enanthate is reported and the literature on sudden respiratory death and phenothiazines is reviewed in an attempt to ascertain if there is a relationship between sudden death due to aspiration or asphyxiation and phenothiazines. The patient was a 49-year-old man diagnosed as suffering from paranoia vera. When his judgment and behavior began to deteriorate, phenothiazine therapy was initiated (37.5mg I.M. every 2 weeks). One month later he complained of multiple side-effects, including generalized stiffness, dry mouth, slurred nasalized speech, drooling, blurred vision, and choking on his food. Examination revealed generalized cogwheel rigidity, slurred speech, a dry mouth and coated tongue, an absent gag reflex, deviation of the tongue to

the right, difficulty in protruding the tongue, and tongue fasciculations. Persistence of these symptoms for almost 2 months, especially the choking on food, led to a decrease in the dose of fluphenazine enanthate to 32.5mg I.M. every 2 weeks. When he was examined a little over a year after the phenothiazine therapy was begun, all side-effects were absent. A review of the English language literature reveals a compilation of 17 reported sudden deaths that might be attributed to aspiration due to a phenothiazine. Nine of the 17 patients, 52.9% showed evidence of possible neurologic disease, and only one had a neurologic disease that could be clearly associated with symptoms of bulbar palsy. Several studies have reported physiologic changes similar to those in the present case, and several theories have been suggested for the development of aspiration in patients being treated with phenothiazines. It is unclear whether phenothiazines are responsible for deaths due to aspiration, but it appears that phenothiazines may cause laryngeal and/or pharyngeal dysfunctions that are responsible for aspiration. 23 references.

003829 Strayhorn, Joseph M.; Nash, James L. Dept. of Psychiatry, Duke University Medical Center, Durham, NC /**A review of neurotoxicity of lithium during therapeutic treatment.**/ Severe neurotoxicity despite "therapeutic" serum lithium levels. Diseases of the Nervous System. 38(2):107-111, 1977.

The reliability of monitoring serum lithium levels to prevent or detect lithium intoxication is critically reviewed with emphasis on factors complicating evaluation and incidence of neurotoxicity. It is concluded that the possibilities of intercurrent medical illness, schizophrenia, a seizure diathesis, a tendency toward increased lithium retention, and some synergistic effect of antipsychotic medications, as well as other possible factors, make it impossible to rely solely on serum lithium levels in establishing dosage. It is likely that the most important means of detecting serious intoxication at an early stage will be a high index of suspicion along with close monitoring of clinical signs. 30 references. (Author abstract modified)

003830 Swett, Chester P., Jr.; Shader, Richard I. McLean Hospital, 115 Mill Street, Belmont, MA 02178 **Cardiac side effects and sudden death in hospitalized psychiatric patients.** Diseases of the Nervous System. 38(2):69-72, 1977.

Psychiatric inpatients (N=1932) were examined to determine the incidence of cardiac side-effects and sudden death, particularly as related to medication. Cardiac side-effects were found to be more common in patients with coexisting cardiac disease than in patients without cardiac disease. Sinus tachycardia occurred in 19 patients, 17 of whom did not have heart disease. Other, less frequently occurring side-effects included arrhythmias, conduction disturbances, and myocardial infarction. In the two cases of sudden death, a causal relationship to drug therapy could not be proved. Neither patient had received tricyclic antidepressants or phenothiazines. 15 references.

003831 Vale, J. A.; Crome, Peter; Volans, Glyn N.; Goulding, Roy. Poisons Unit, New Cross Hospital, London SE14, England **Dangers of dextropropoxyphene.** British Medical Journal (London). No. 6066:975, 1977.

In a letter to the editor in response to an article on the potential seriousness of dextropropoxyphene poisoning, a specific antagonist of dextropropoxyphene is presented. Cerebral and cardiorespiratory depressive effects that may follow an overdose of dextropropoxyphene can be prevented or abolished by naloxone. Repeated doses of this safe and specific antagonist may be required as the duration of action of dextropropoxyphene exceeds that of naloxone. 3 references.

003832 Waldmann, E.; Horsfall, P. A. L. no address **Pentazocine addiction: a warning.** British Medical Journal (London). No. 6061:642, 1977.

In a letter to the editor attention is drawn to pentazocine addiction. By 1971 130 reports of alleged dependence on oral as well as parenteral pentazocine had been received from worldwide sources. A case history of the development of physical drug dependence and serious withdrawal syndrome in a 50-year-old physician who suffered from recurrent abdominal pain is presented. Necessity for caution is emphasized when prescribing pentazocine particularly since pentazocine is generally regarded as a potent, nonaddictive analgesic and is exempt from international narcotics legislation. 5 references.

003833 Wallace, Edwin R., IV; Staton, Marshall A. Yale Psychiatric Institute, PO Box 12 A, Yale Station, New Haven, CT 06520 **Acute hypertension after abrupt withdrawal of antipsychotic medication.** Southern Medical Journal. 70(4):395, 1977.

A case report of an 18-year-old patient with catatonic schizophrenia who developed acute hypertension when administration of haloperidol was discontinued is presented. Elevated blood pressure was sustained for 3 days until it was discovered that intramuscular administration of benztropine mesylate immediately reduced it to normal. The fact that the hypertension was not noted earlier while the patient was receiving the antipsychotic drugs suggests that it was a withdrawal phenomenon. 4 references. (Author abstract modified)

003834 Watson, Joyce M. Greater Glasgow Health Board, Glasgow, Scotland /**Hydrocarbon or solvent inhalation.**/ Glue-sniffing in profile. Practitioner (London). 218(1304):255-259, 1977.

Glues-niffing, also referred to as hydrocarbon or solvent inhalation, which an increasing number of children in Lanarkshire, Glasgow, Renfrewshire, and Ayrshire have adopted as the latest fad, is reviewed. Sources of referral to physicians and the agents used experimentally for inhalation are discussed briefly. Children and young persons predominate in solvent abuse, the age range being 8 to 17 years in most places; boys, on average, outnumber girls around 10 to 1. In the main, solvent sniffing is a group activity, closely associated with high rates of truancy and poor scholastic performance. The progressive development of symptoms during an episode of hydrocarbon inhalation was listed in a table and compared with the progressive stages of anesthesia. The conflicting data on the toxicity of solvents used deliberately for inhalation was reviewed. Reports of development of tolerance and habituation or physical dependence were mentioned. 26 references.

003835 Weiner, William J.; Nausieda, Paul A.; Swisher, Charles; Klawans, Harold L. no address **Methylphenidate-induced chorea.** Neurology. 27(4):391, 1977.

At a meeting of the American Academy of Neurology in Atlanta, GA in April, 1977, methylphenidate induced chorea was studied in a child with minimal brain dysfunction and guinea pigs. The study of the child clearly indicated that the movement disorder was methylphenidate induced and that the drug effect was related to the major central effect of methylphenidate. A guinea pig behavioral model of dopamine

related stereotyped behavior was employed to assess the ability of chronic methylphenidate to induce receptor site hypersensitivity. After 3 weeks of chronic methylphenidate, animals demonstrated a hypersensitive response to apomorphine. The results suggest that chronic methylphenidate is capable of producing receptor site hypersensitivity. It was suggested that in children with minimal brain dysfunction in whom chorea ensures shortly after initiation of methylphenidate therapy, the abnormal involuntary movements are probably related to the drug's central dopaminergic effect, and that in children in whom choreiform movements develop after chronic methylphenidate treatment, the drug may produce altered straital dopamine receptor site responsiveness that results in chorea.

003836 Wolpert, Edward A. Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital, 2959 South Ellis Avenue, Chicago, IL 60616 **Nontoxic hyperlithemia in impending mania.** American Journal of Psychiatry. 134(5):580-582, 1977.

The case of a patient with prodromal symptoms of mania that led to hyperlithemia (reaching a serum level of 4.5mEq/liter) with no psychological, physiological, or electrolyte abnormalities is reported. The patient was a 26-year-old woman who had been taking lithium carbonate for about a year. It is hypothesized that the presence of prodromal symptoms indicates a state in which lithium transport is interfered with temporarily and high serum lithium levels can occur without lithium entering cells where toxic effects would occur. It is suggested that in the treatment of manic-depressive illness with lithium carbonate, the clinical state of the patient is of greater importance than usual laboratory values of toxicity. 6 references. (Author abstract modified)

003837 Young, R. E.; Ramsay, L. E.; Murray, T. S. Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, Scotland **Barbiturates and serum calcium in the elderly.** Postgraduate Medical Journal. 53(618):212-215, 1977.

A retrospective study was conducted on a biochemical survey of people aged 65 and over in a general practice to seek evidence that barbiturate treatment in the elderly for indications other than epilepsy may adversely affect vitamin D metabolism. Comparison of three subgroups taking barbiturates, nitrazepam or diazepam, and none of these, respectively, showed that the barbiturate group had a significantly lower serum calcium concentration than did those taking nitrazepam or diazepam. It is probable that the barbiturate use was associated with use of barbiturate at low or moderate dosage, such as is given for hypnotic rather than anticonvulsant purposes. Barbiturate treatment in the elderly may influence vitamin D metabolism adversely; clinicians should be alert to the possibility of osteomalacia in such patients. 13 references. (Author abstract modified)

003838 Zumoff, Barnett; Hellman, Leon. Clinical Research Center, Montefiore Hospital and Medical Center, 111 E. 210th St., Bronx, NY 10467 **Aggravation of diabetic hyperglycemia by chlordiazepoxide.** Journal of the American Medical Association. 237(18):1960-1961, 1977.

The administration of chlordiazepoxide hydrochloride, 40mg daily, aggravated the hyperglycemia in an insulin dependent, maturity onset diabetic woman, raising the fasting blood glucose values from 220mg/100 ml to 380mg/100 ml. Review of the literature shows that virtually all psychoactive drugs affect diabetes; most tranquilizers aggravate diabetic hyperglycemia, while most antidepressants ameliorate it. The effect described in this communication is of clinical importance because of the widespread use of the benzodiazepine tranquilizers. 12 references. (Author abstract)

16 METHODS DEVELOPMENT

003839 Gringras, M. no address **Experiences with some new scales for use in general practice trials.** Journal of International Medical Research (Northampton). 5(Supplement 1): 61-65, 1977.

At a symposium held at Rabat, Malta, in November, 1976, experiences with a newly developed technique for measuring depressive symptoms were described. A pilot trial was made of the General Health Questionnaire, a series of visual analogue scales with a central reference point, in conjunction with a new formulation of clomipramine. Use of the scales appeared to be somewhat more time consuming and rigid adherence frequently did not reflect important symptoms. However, it was judged easier to use and it is suggested that with some modification could be a useful and accurate instrument for the general practitioner. 1 reference. (Journal abstract modified)

003840 Kellner, Robert; Simpson, George M.; Sheffield, Brian F. University of New Mexico, School of Medicine, Albuquerque, NM 87106 **The value of self-rating scales in drug trials.** Psychopharmacology Bulletin. 13(2):42-43, 1977.

In a paper presented to a meeting of the American College of Neuropsychopharmacology (ACNP), at San Juan, PR, in December 1975, the results of several studies, some of which were designed to compare the effectiveness (sensitivity) of rating and self-rating scales in detecting differences between the effects of psychotropic drugs and placebo, are discussed. The sensitivity of the scale was affected by several features, such as the type of symptoms, the time focus, the form of the question and the cues available for self-rating. A conventional box scale in which cues, such as "not at all," are printed on the top of the page appeared to be less sensitive than a form on which the cues were printed on a horizontal graphic scale. Questionnaires and checklists were, in an average clinic population, somewhat more effective than self-rating scales that required scoring depending on severity or frequency. Self-ratings with the aid of test cards appeared to be somewhat more sensitive than the conventional pencil and paper versions. The results suggest that with the present knowledge of psychometrics it is possible to construct self-rating scales that are as sensitive or perhaps more sensitive than ratings by expert raters. 5 references.

003841 Marcos, Luis R.; Goldberg, Eleanor; Feazell, David; Wilner, Milton. Dept. of Psychiatry, New York University Med. School, 550 1st Avenue, New York, NY 10016 **The use of sodium amytal interviews in a short-term-community-oriented inpatient unit.** Diseases of the Nervous System. 38(4):283-286, 1977.

The use of interviews during medication with sodium amytal in 31 patients in a short-term community oriented inpatient unit is discussed. Patients presenting with severe inhibition and uncommunicativeness, whether from organic disease, manic-depressive illness, psychotic depressive reaction, hysteria, or diverse types of schizophrenia, are often difficult to diagnose and, hence, to treat. The use of sodium amytal interviews has been shown to be exceptionally helpful in distinguishing schizophrenic catatonic stupors from severe depressive reactions associated with catatonia like symptomatology and in

identifying the underlying dynamics of the patients. Information elicited about past psychiatric history, family history, and the onset of the illness have proven important in planning the treatment program. The observation that, when the patient shows marked disinhibitory changes during amytal interview, a better prognosis can be predicted, is supported. The psychiatric unit is described and the details of interview planning, obtaining patient consent, techniques, and interview evaluation are described. One case history is documented. 42 references.

003842 Ramsay, Anna; Ballinger, Brian R.; Millar, Anne Y.; Stewart, Michael J. Drug Monitoring Unit, Royal Dundee Liff Hospital, Dundee, Scotland **Individual drug supply in a psychogeriatric ward: an evaluation of the system.** Nursing Times (London). 73(15):537-539, 1977.

To determine possible advantages of an individual patient drug supply system over a ward stock system, the relative nurse and pharmacist time, and the degree of observed and urine tested drug discrepancies were assessed for both methods during a 6 week period on a 60 patient psychogeriatric ward. Analysis of data indicated that the amount of staff time required for prescription and administration was doubled by the individual patient supply system. While fewer drug discrepancies were observed for the individual supply system, urinalysis indicated no significant differences between the methods. It is concluded that no definite advantages could be determined for the individual patient supply system, although many staff members found this method preferable to the ward stock system. 3 references.

003843 Uhlenhuth, E. H.; Turner, David A.; Purchatzke, Gerald; Gift, Thomas; Chassan, Jack. University of Chicago, 950 East 59th Street, Chicago, IL 60637 **Intensive design in evaluating anxiolytic agents.** Psychopharmacology (Berlin). 52(1):79-85, 1977.

Primarily anxious, psychoneurotic patients (N=15) were administered either diazepam or placebo to investigate the usefulness of intensive design in detecting the effects of established antianxiety agents in single patients studied for brief periods and the utility of combining intensive and extensive designs by jointly analyzing the results from several similarly treated patients. Patients were treated for 8 weeks, divided into four 2-week blocks, within which patients received diazepam 1 week and placebo the other, with the order determined at random. Psychological evaluations included the Hopkins Symptom Checklist (HSC), Hamilton Anxiety Scale, Profile of Mood States (POMS), and reports of occupational and social functioning. These and other anxiety measures clearly recorded the antianxiety effect of diazepam. The most sensitive criteria distinguished diazepam from placebo even when results were considered from the first patients during their first 4 weeks of treatment. It is suggested that intensive design overcomes drawbacks of extensive design and offers the possibility of efficiently developing predictors of response to pharmacotherapy. 23 references. (Author abstract modified)

17 MISCELLANEOUS

003844 Adams, P. Evans. Dept. of Psychiatry, Temple University Health Sciences Center, Philadelphia, PA **Pharmacologic management of psychiatric emergencies.** Pennsylvania Medicine. 80(2):49-52, 1977.

Types, etiologies, and treatments of psychiatric emergencies are reviewed with an emphasis on drug induced emergencies and appropriate pharmacologic treatments for drug induced or drug influenced emergencies and functional psychoses are suggested. The following acute syndrome producing agents are discussed: alcohol, LSD, marijuana, mescaline, amphetamines, darvon, heroin, methadone, barbiturates, and phencyclidine. Diagnosis and treatment of coma and seizure patients are described. Emergencies arising from the use of major tranquilizers and tricyclic antidepressants are presented. Antipsychotic and sedating drugs use in emergency situations involving functional psychoses is discussed. It is concluded that the mental health professional should be thoroughly informed and careful in patient condition evaluation in order to safely and effectively reduce painful or dangerous symptomatology. The possibility of physical factors contributing to or creating the presumed psychological picture may be questioned. 17 references.

003845 Ananth, J. St. Mary's Hospital, 3830 La Combe Avenue, Montreal, P.Q., Canada **Treatment of obsessive compulsive neurosis: pharmocological approach.** Psychosomatics. 17(4):180-184, 1977.

In a review of the pharmacological approach to treating obsessive-compulsive neurosis, the use of anxiolytic, antiobsessive, and antidepressant drugs, and biochemical approaches in general are reviewed. The selection of the appropriate drug depends on the psychopathological profile. Anxiolytics (chlordiazepoxide, oxazepam, diazepam, bromazepam, and lorazepam) relieve the coexistent anxiety, and antidepressants (primarily the tricyclics) relieve the secondary depression. The monoaminoxidase inhibitors are generally regarded as not useful in pure obsessional states, while doxepin and amitriptyline have been found to have useful but unpredictable effects. However, there are indications that haloperidol and chlorimipramine may have antiobsessive effects. The latter is the recommended drug of choice. A study to substantiate the antiobsessive effect of the serotoninergic substance, tryptophan, as in progress. 54 references.

003846 Ananth, J.; Luchins, D. St. Mary's Hospital, 3830 Lacombe Avenue, Montreal, Quebec H3T 1M5, Canada **A review of combined tricyclic and MAOI therapy.** Comprehensive Psychiatry. 18(3):221-230, 1977.

The available data on the combined use of monoamine oxidase inhibitors and tricyclic antidepressants, their therapeutic efficacy, and the occurrence of toxic syndrome, are critically reviewed in order to place this mode of treatement in a proper perspective. It appears that combined antidepressant therapy, if properly administered, leads to neither serious complications nor to an inordinate number of side-effects. The clinical usefulness of this treatment, however, is not conclusively proven. It is suggested that controlled studies comparing combined therapy will help to determine whether combined therapy is useful in refractory cases, depression in general, or any subcategory of depression. 47 references.

003847 Baron, Miron. no address **Melatonin, MSH, and psychosis.** American Journal of Psychiatry. 134(5):583, 1977.

In a letter to the editor, conclusions regarding the neurochemical effects of melatonin reported in "Negative Effects of Melatonin on Depression" by John S. Carman et al. are rebutted. Research data inconsistent with the conclusions are: 1) chlorpromazine has been shown to enhance the accumulation of melatonin in animal models by a peripheral inhibition of its breakdown, so neuroleptics may increase, rather than decrease, the net availability of melatonin in the CNS; 2) melatonin eliminates the mechanism that opposes the action of melanocyte stimulating hormone (MSH) inhibitory factor (MIF) and increases MSH release from the pituitary, consistent with high, rather than low, melatonin levels; 3) the cyclization of 5-methoxytryptamine, a melatonin related compound, to the psychotomimetic methoxyharmalan has been a matter of controversy; 4) the increase in central serotonin and gamma-aminobutyric acid turnover occurring with melatonin administration can represent a mechanism other than a compensatory response to a primary blockade of receptors; 5) no mention was made of two double-blind studies indicating an ameliorative effect of pineal extract on chronic schizophrenia; melatonin related compounds may have been involved. 9 references. (Author abstract modified)

003848 Bassus, Jacques; Pacheco, Henri; Legheand, Jacques. Service de chimie biologique, Batiment 406, I.N.S.A., 20, avenue Albert Einstein, F-69621 Villeurbanne, France **/Potential psychotropics. XII. Synthesis and structure of new butyrophenones with a 1,3-dioxa 9-aza spiro(5.5) undecane ring, having neuroleptic activity./** Psychotropes potentiels. XII. Synthese et structure de nouvelles butyrophenones a cycle dioxa-1,3 aza-9 spiro (5.5) undecane, douees d'activite neuroleptique. European Journal of Medicinal Chemistry (Paris). 12(1):35-40, 1977.

The synthesis of eight new 4-fluorobutyrophenones with a 1,3-dioxa 9-aza spiro (5.5) undecane ring were synthesized, the conformation of the ring determined, and the neuroleptic activity of seven of the compounds studied in mice and rats. The eight compounds were substituted in the 5 and 2 positions of the undecane ring as follows, 1) H, H; 2) methyl H; 3) ethyl, H; 4) methyl, methyl; 5) ethyl, 4-fluorophenyl; 6) ethyl, 4-chlorophenyl; 7) ethyl; 3-fluorophenyl and 8) ethyl, methyl. Seven of the compounds (not 4 above) were compared to haloperidol in the following tests: 1) inhibition of reflexes of posture (rotarod) and grip (traction); 2) decrease of mortality induced by amphetamine; 3) augmentation of the hypnogenic effect of pentobarbital; and 4) protection from convulsions induced by electroshock or pentetrazol. Qualitatively, the seven compounds resembled haloperidol in activity in the above tests, but the intensity of the effects was weaker than that of halperidol. The lethal dose 50 of compounds 3 and 6 were comparable to haloperidol when administered intraperitoneally, but the other compounds were 2 to 5 times more toxic. In rats, the 7 compounds induced hypothemia comparable to haloperidol and the intensity and duration of their cataleptigenic effect were comparable to haloperidol with the exception of compounds substituted with 4-chlorophenyl or 3-fluorophenyl in position 2. Compounds 1, 2 and 3 were more effective than compounds 5, 6, 7, and 8 in antagonizing the stereoptyped movements induced by dexamphetamine. 28 references.

003849 Boethius, Goran; Nordgren, Lars; von Scheele, Christian. Department of Medicine, General Hospital, S-831 01 Ostersund, Sweden **A five-year survey of purchases of antacids, anticholinergic and psychotropic drugs.** Journal of Psychosomatic Research (Oxford). 21(1):33-39, 1977.

Data were compiled from prescriptions of drugs used in peptic diseases and of psychotropic drugs to determine if those treated for peptic diseases might be expected to disclose psychiatric disability. Patients who received antibiotics served as a control group. All patients were followed for a 5 year period. Those treated for peptic diseases purchased significantly higher amounts of psychotropic drugs than the controls. There seem to be three patterns of purchases by patients treated for peptic diseases: one shows a rapid and marked decline in purchase of drugs used in peptic disease; one shows a steady and continuous purchase of psychotropic drugs, and one shows an alternating purchase of drugs used in peptic diseases and psychotropic drugs. On the assumption that psychotropic drugs are purchased by mentally decompensated patients, the purchase pattern in the last mentioned group might indicate that overt as well as covert anxiety plays an important role in those seeking medical advice because of complaints related to peptic diseases. A psychosomatic approach to the patient rather than to the disease thus seems justified. 14 references. (Author abstract modified)

003850 Branson, Roy. Kennedy Institute, Center for Bioethics, Georgetown University, Washington, DC **Prison research: national commission says "no, unless...."** Hastings Center Report. 7(1):15-21, 1977.

The recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research are examined. The considerations that entered into the commission's decision included data on the extent of experimentation in prisons, questions of the utility of such experiments, questions of prisoners' rights, and ethical considerations. In sum, the commission decided that such research on prisoners should not be conducted unless: 1) there are compelling reasons to involve prisoners; 2) conditions of equity are satisfied; and 3) there is a high degree of voluntariness on the part of prisoners and openness in the prison. Text of the commission's recommendations is included. 36 references.

003851 Briant, Robin H. Auckland Hospital, Auckland, New Zealand **Drug treatment in the elderly: problems and prescribing rules.** Current Therapeutics (Seaforth). 18(2):41-42, 44-45, 47, 1977.

The elderly are viewed as particularly susceptible to side-effects of medications, especially to such drugs as digoxin, various diuretics, antihypertensive agents, beta adrenoceptor blocking agents, oral hypoglycemic agents, powerful antiinflammatory agents, benzodiazepine, and hypnotics. The aging should be given as few drugs as possible and only for so long as necessary. Prescribing rules for the elderly include definition of a clear and rational therapeutic goal, review of all medications for possible interactions, establishment of a simple regimen, choice of optimum dosages of the safest available compounds, verification that the patient understands and is competent to handle his medications, and stopping of any unnecessary drug. 2 references.

003852 Carpenter, William T., Jr.; McGlashan, Thomas H.; Strauss, John S. Schizophrenia Research, New York State Psychiatric Institute, 722 West 168th St., New York, NY 10032 **The treatment of acute schizophrenia without drugs: an investigation of some current assumptions.** American Journal of Psychiatry. 134(1):14-20, 1977.

A hospital program for acute schizophrenic patients that emphasizes psychosocial treatment and sharply limits the use of medication is described, and the course of 49 patients in the program is compared to that of 73 patients receiving "usual" treatment of predominantly drug therapy. The psychosocial therapy used in the treatment program was a milieu approach based on the philosophy that self-understanding and social adaptation are fundamental to recovery from psychotic episodes. Group therapy, family therapy, and individual psychoanalytically oriented therapy were used. Followup of the patients in this program, which was conducted at the National Institutes of Health (NIH) at one year and the other group at two years demonstrated a small but significantly superior outcome for the NIH cohort. In addition, the 22 NIH patients receiving medication and the 27 drug free patients had similar outcomes at one year. The authors discuss the feasibility of treating acute schizophrenic patients with minimal use of medication. 41 references. (Author abstract modified)

003853 Colpaert, Francis C. Department of Pharmacology, Janssen Pharmaceutica Research Laboratories, B-2340 Beerse, Belgium **Narcotic cue and narcotic state.** Life Sciences. 20(7):1097-1108, 1977.

In a review on narcotic cue (NC) and narcotic state (NS), data on stimulus control by narcotic analgesic drugs is discussed. The following conclusions are drawn: 1) narcotic analgesics possess discriminative stimulus properties (NC) and are able to produce a state upon which responses can be made conditional (NS); 2) the NC is adequately defined as the discriminative stimulus complex exclusively associated with the specific central actions of narcotic analgesic drugs; 3) the NC contains a significant though not critical dopaminergic component; 4) the NC is not subject to tolerance; 5) the NC, as defined by drug discrimination methods in animals, is intimately related to the subjective experiences induced by narcotics in humans; 6) the study of the cueing properties of narcotic analgesics is relevant to the preclinical evaluation of the abuse liability of these drugs; 7) the NS is critically dependent on the integrity of central 5-hydroxytryptaminergic neurotransmission; 8) the NS is subject to tolerance; and 9) the NC and NS are two different phenomena. 96 references. (Author abstract modified)

003854 Cusano, Paul P.; Mayo, Julia; O'Connell, Ralph A. no address **The medical economics of lithium treatment for manic-depressives.** Hospital & Community Psychiatry. 28(3):169, 173, 1977.

The economic aspects of lithium carbonate treatment for manic-depressive psychoses are discussed. The cost effectiveness figures for a lithium clinic at St. Vincent's Hospital and Medical Center of New York are provided. The clinic has operated in a teaching hospital setting for more than eight years, and has served more than 100 patients. The mean annual hospital cost for patients not treated with lithium was calculated to be $2046. The hospital cost for lithium treated patients is $399; the clinic cost is $620. The annual medical costs with lithium thus amount to less than half the expected cost without lithium. Results show that lithium has been of economic value to the patient, his family, and to the community. 4 references.

003855 Dankova, Jana; Boucher, Rene; Poirier, Louis J. Laboratoires de Neurobiolgie, Faculte de Medecine, Universite Laval, Quebec, Canada **Effects of 1694 and other**

dopaminergic agents on circling behavior. European Journal of Pharmacology (Amsterdam). 42(2):113-121, 1977.

The effects of amineptine chlorydrate (1694) (AMC) on brain monoamines in rats and its efficacy in inducing circling behavior in comparison to the effects of other dopaminergic agents in rats and cats were studied. Administration of AMC increased the concentration of homovanillic acid in the striatum, but had no significant effect on the concentrations of dopamine, noradrenaline, 5-hydroxytryptamine, and 5-hydroxyindoleacetic acid in the striatum, cortex, thalamus/hypothalamus, or pons/midbrain of rats. Unilateral lesioning at the level of the entopeduncular nucleus in cats and rats caused spontaneously occurring ipsiversive circling behavior; however, circling was more sustained in cats. AMC was more active than L-dopa and piribedil and less active than apomorphine, d-amphetamine and methamphetamine in exaggerating the ipsiversive circling. In higher doses, AMC increased exploratory activity, but it was not associated with any stereotypy. Removal of the contralateral motor cortex in the cat abolished spontaneous and drug induced circling movements. The results support the idea that these dopaminergic agents act on the striopallidal system of the intact side which is no longer properly counterbalanced by the corresponding system of the lesioned side. 20 references. (Author abstract modified)

003856 DeLiz, Antonio J. 218 W. Stewart Ave., Garden City, NY 11530 **Meditation, protein, diet, and megavitamins in the treatment of a progressive, iatrogenic cardiac and psychotic condition.** Journal of Orthomolecular Psychiatry. 6(1):44-49, 1977.

An orthomolecular psychiatrist recounts his personal experiences of physical discomfort due to a cardiovascular problem with angina and high blood pressure and his reactions to conventional treatment which included a drug induced schizophrenic syndrome. After researching his prescribed medication, the physician concluded his mental symptoms were caused by the drugs (propanolol and alphatocopherol) he was taking. He placed himself on a salt free, sugar free, and starch free diet with high amounts of vitamins (niacinamide, vitamin E, and vitamin C) and fat free meats and fish. By the end of 8 weeks he was free from anginal pain, the partial occlusion of the left posterior tibial artery, and the mental condition. 17 references.

003857 Docherty, John P.; Marder, Stephen R.; Van Kammen, Daniel P.; Siris, Samuel G. Veterans Administration Hospital, West Spring Street, West Haven, CT 06516 **Psychotherapy and pharmacotherapy: conceptual issues.** American Journal of Psychiatry. 134(5):529-533, 1977.

Conceptual issues regarding maintenance of an integration of psychotherapeutic and pharmacotherapeutic treatment are discussed with focus on the problem of bimodal relatedness, that is, the distinction between relating to the patient as a diseased organ or object of study and as a disturbed person. Forces that act to emphasize one mode or the other inappropriately are isolated, and major difficulties arising from a failure to maintain bimodal relatedness are described. It is suggested that, in a setting of combined therapy, maintaining and safeguarding the optimal relationship of collaborative subject/subject relatedness can prevent the emergence of problems destructive to effective psychiatric treatment and research. Suggestions for maintaining such a relationship are presented and illustrated with a case example. 13 references. (Author abstract modified)

003858 Fann, William E.; Karacan, Ismet; Pokorny, Alex D.; Williams, Robert L. Department of Psychiatry, Baylor College of Medicine, Houston, TX **Phenomenology and treatment of depression.** New York, Spectrum, 1977. 350 p. $20.00.

The phenomenology and treatment of depression are considered in papers collected from the proceedings of a symposium, held at Baylor College of Medicine in Houston in December, 1975. Approximately half the 22 papers are concerned with depression phenomenology and etiology, while the others relate primarily to depression treatment. Areas discussed include the biochemical, metabolic, and neurological aspects of depression; depression in women; depression as a result of life change; current psychoanalytic concepts of depression; suicide; diagnostic aspects of depression; pharmacological treatment; electroseizure therapy; crisis and outpatient management; and the combination of depressive and addictive syndromes.

003859 Fink, Max. Psychopharmacology Research Laboratory, SUNY at Stony Brook, School of Medicine, Stony Brook, NY 11790 **EST: a special case in pharmacotherapy.** In: Fann, W., Phenomenology and treatment of depression. New York, Spectrum, 1977. 350 p. (p. 285-294).

In a paper presented to a symposium on Phenomenology and Treatment of Depression held at Baylor University in December, 1975, the present state of knowledge regarding electroseizure therapy (EST) is summarized, and a psychopharmacologic model is proposed. It is suggested that significant parameters of the treatment are well understood, i.e. that the process is neither purely psychological nor physiological and neither convulsion nor shock is essential; the biochemical changes which are the basis for improvement are closely related to the changes induced by the drug therapies, and the modes of action appear to be likewise related. EST is seen as a special psychopharmacologic intervention in which increases in central neurohumors and hypothalamic peptides augment the levels of these substances which occur in the pathologic process. The advantages of the psychopharmacologic model for the study of EST are enumerated. 22 references.

003860 Furst, Z.; Foldes, F. F.; Knoll, J. Department of Anesthesiology, Montefiore Hospital and Medical Center, Bronx, NY 10467 **The influence of naloxone on barbiturate anesthesia and toxicity in the rat.** Life Sciences. 20(6):921-926, 1977.

The influence of naloxone on barbiturate anesthesia and toxicity was studied in rats. Naloxone significantly delayed the development and decreased the duration of the loss of righting reflex caused by 35mg/kg intraperitioneally or subcutaneously administered pentobarbital or intraperitoneally injected methohexital. Naloxone also antagonized the toxicity of 50 to 125mg/kg intraperitoneally administered pentobarbital and approximately doubled the LD50 of pentobarbital. The results suggest that therapeutic trials with relatively large doses of naloxone are justifiable in patients intoxicated with barbiturates. 33 references. (Author abstract modified)

003861 Gershon, Samuel; Angrist, Burton; Shopsin, Baron. Neuropsychopharmacology Research Unit, Department of Psychiatry, New York University Medical Center, New York, NY 10016 **Pharmacological agents as tools in psychiatric research.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 65-93).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniver-

sary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel, in December 1975, studies of the effects of L-DOPA, CNS stimulants (amphetamine, methylphenidate), dopamine receptor stimulants (apomorphine, ET-495), monoamine oxidase inhibitors, imipramine, lithium, and an anticholinesterase agent (diisopropyl fluorophosphonate) on nonpsychotic subjects, schizophrenic patients, and manic-depressive patients are reviewed. The studies revealed that these drugs can produce reaction patterns based on the preexisting psychopathology (i.e. induction of psychoses and/or exacerbation of symptoms in schizophrenic patients; induction of manic episodes in manic-depressive patients) as well as inducing psychotic states or depressions in normal or nonpsychotic subjects. Similar psychopathological reactions occurred within subject groups despite the fact that different central neurotransmitter systems were being affected by the various drugs. Several illustrative case histories are presented. It is suggested that a unitary concept of neurotransmitter involvement in these mental diseases is inadequate. It is also suggested that a continuum does not exist across diagnoses, but that there is a continuum in those predisposed individuals from normal to manifest illness. The findings are discussed in terms of their diagnostic value and of their implications for current theories of psychoses. It is strongly suggested that massive manipulation of one neurotransmitter system probably affects other neurotransmitter systems secondarily. 95 references.

003862 Glatt, M. M. St. Bernard's Hospital, Southall, Middlesex, England **Abuse of solvents "for kicks."** Lancet (London). No. 8009:485, 1977.

In a letter to the editor, a new form of solvent sniffing and inhaling by 10 men (18-22-years-old) who had come across paint thinner while working in a prison shop is described. The effects which resembled a short-lived drunk state -- dizziness, unreality, "clouded mind", slight excitement -- started within a few minutes and lasted 15 to 30 min unless sniffing was sustained or resumed after an interval. Among the prisoners who had tried other drugs, six were asked to rank them according to their preference; all put thinners at the bottom of the list, directly behind alcohol. The use of the solvent (methylethylketone) was discontinued and no cases were seen in this prison after 1969, but other cases of "thinner addiction" have been described among children and adolescents in the U.S.A. and Sweden, with similar symptoms.

003863 Goodwin, Frederick K.; Cowdry, Rex W.; Webster, Marion H. Section on Psychiatry, Laboratory of Clinical Science, NIMH, Bethesda, MD 20014 **Predictors of drug response in the affective disorders: toward an integrated approach. (Unpublished paper).** Rockville, MD, NIMH, 1977. 29 p.

The relationship between pretreatment biological measures and subsequent response to specific drug treatments is discussed. Studies are reviewed which are laying the groundwork for a more rational and integrated approach to the prediction of drug response in the major affective disorders. Hypotheses guiding research in affective illness (the amine hypotheses and hypotheses involving other biological parameters, such as membrane electrolyte function, neuroendocrine function, and electrophysiologic measures such as the average evoked response) are reviewed. A model for explaining interrelationships among clinical, biological, and pharmacological variables is presented and it is pointed out that any findings in the biological and pharmacological spheres must take into account the unipolar/bipolar distinction in depression. For each of the major sets of variables, sources of variance in the data are described and prominent findings with regard to predictors of drug response are presented. Tentative conclusions about future research directions are offered. 55 references.

003864 Greist, John H.; Jefferson, James W.; Combs, Ann M.; Schou, Mogens; Thomas, Ann. Department of Pscyhiatry, University of Wisconsin, Center for Health Sciences, Medical School, 1300 University Ave., Madison, WI 53706 **The lithium librarian: an international index.** Archives of General Psychiatry. 34(4):456-459, 1977.

A computerized literature search service for publications dealing with lithium salts is reported. Lithium salts are being widely used for treatment and prophylaxis of bipolar affective disorder (manic-depressive psychosis) and are under investigation in more than 30 other illnesses. The relevant literature has grown from 43 articles published between 1949 and 1964 to nearly 4000 today. A computer based lithium librarian program has been developed that provides an updated registry of all lithium references, rapid search capability, constant availability, and easy transferability to identical computer systems located on three continents. References provided by the system are more complete, more rapidly available, and less costly than references obtained from other bibliographic services. This specific response to the rapidly expanding lithium literature provides a model for comprehensive acquisition and searching of other specialized subject areas needed by clinicians and researchers. 12 references. (Author abstract modified)

003865 Grimsson, Almar; Olafsson, Olafur. Pharmaceutical Division of the Ministry of Health and Social Security, Reykjavik, Iceland **Drug prescription in Iceland.** British Journal of Preventive & Social Medicine (London). 31(1):65-66, 1977.

Two ad hoc surveys on drugs prescribed in Reykjavik during November, 1972, and November, 1974, were made: 1) to collect information on doctors' prescribing habits and on drug use or abuse by the recipient; 2) to provide a tool for the health authorities so that drug prescriptions could be controlled and the use of drugs monitored; and 3) to provide statistics on drug taking for the use of those studying drug addiction. After the first survey a publicity campaign was launched and doctors were encouraged to change their prescribing habits; only minor changes in doctors' prescribing habits were noticed, although it is realized that this type of program will require a longer period to prove its effectiveness. The surveys showed that benzodiazepines are more widely prescribed than chlorodiazepoxide. Doctors have been warned of the probable addictive effect of benzodiazepines (Grimsson, 1974). Drug addicts who formerly went from one clinic to another have now been identified, and they can only receive drugs on prescription from their own family doctor or his deputy. 4 references. (Journal abstract modified)

003866 Gringras, M.; Luscombe, D. K.; Jones, R. B.; Beaumont, G.; Sedrup, J.; John, V. no address **A clinical trial of a 50mg formulation of clomipramine (Anafranil) with steady-state plasma level measurements.** Journal of International Medical Research (Northampton). 5(Supplement 1):119-124, 1977.

At a symposium held at Rabat, Malta, in November, 1976, twenty depressed patients seen in general practice were admitted to an open, uncontrolled pilot trial of a new 50mg formulation of clomipramine with steady state plasma measurements. Treatment was administered for four weeks and clinical progress assessed by the General Health Questionnaire, a new depression rating scale and a new design of a visual analogue scale. Plasma levels of clomipramine and desmethyl-

clomipramine were assayed. Steady state appeared to be achieved between one and two weeks. The 50mg formulation of clomipramine appeared to produce therapeutic levels in 17 of the 18 patients treated. Because so many patients recovered in spite of individually variable plasma levels no correlations between clinical effect and plasma levels were demonstrable. Side-effects were not generally troublesome and were low in incidence. Correlations between plasma level and side-effects were inexplicably negative but rarely significantly so. 2 references. (Journal abstract modified)

003867 Haidri, Nazar H.; Gazzillo, Frank L. Department of Neurosciences, New Jersey Medical School, Newark, NJ **Newer concepts in management of migraine headaches.** Journal of the Medical Society of New Jersey. 74(1):11-14, 1977.

Newer concepts in the management of migraine are reviewed with special emphasis on prophylactic therapy. When simple analgesics do not suffice, one usually proceeds to ergotamine. Frequent attacks call for prophylaxis or interval therapy. The most common drugs here are the slow release ergot preparations, methysergide, and propanolol. Pizotifen and clonidine are little used but may be promising in the future. Also employed are cyproheptidine, levodopa, phenytoin, and monoamine oxidase inhibitors, and coticosteroids. The main effects and side-effects of each drug are described. Supportive therapy includes control of sensitizing environmental factors and in some cases treatment of underlying psychiatric disorders. 20 references.

003868 Hassar, M.; Pocelinko, R.; Weintraub, M.; Nelson, Dorothy; Thomas, Gordon; Lasagna, L. no address **Free-living volunteer's motivations and attitudes toward pharmacologic studies in man.** Clinical Pharmacology and Therapeutics. 21(5):515-519, 1977.

To ascertain free living volunteers' motivations and attitudes toward pharmacologic studies in man, 2 groups of volunteers who had participated in pharmacologic studies were interviewed about their motivation and their impressions of such studies. One group was from a university community, the other from the pharmaceutical industry. The differences between the two groups were correlated with their respective backgrounds. Both groups had favorable impressions about drug studies and investigators. Most were satisfied with the information given them about the nature and risks of the studies, but some believed that a written description of the study that they could consult at home would improve their understanding of the information. Financial reward was the primary reason given by both groups for volunteering, but the perceived risk of the study was the ultimate deciding factor. The volunteers disliked having their mobility restricted and for this reason might not be willing to participate in long-term studies, such as those formerly carried out in prisons. Alternative sources of volunteers for long-term studies will have to be found. 3 references. (Author abstract)

003869 Hatfield, Frank. University of California, Davis, CA 95616 **Prison research: the view from inside.** Hastings Center Report. 7(1):11-12, 1977.

The practical and psychological factors relating to prisoners' participation in medical research are described by a former participant in a program operated by the Solano Institute for Medical and Pharmacological Research (SIMPR). SIMPR conducts tests dealing with tolerance for substances in humans and with clinical investigation. It is pointed out that participation in medical research offers the prisoner monetary and emotional returns and can give him a sense of purpose. It is argued that this means of gaining money and human dignity should not be denied to prisoners unless a reasonable alternative can be offered.

003870 Herrmann, W. M.; Beach, R. C. Department Klinische Neuropsychopharmakologie, Schering AG, Postfach 650311, D-1000 Berlin 65, Germany /**Neuropsychopharmacological models for objective assessment of central effects of hormones.**/ Neuropsychopharmakologische Modelle zur Objektivierung zentraler Wirkungen von Hormonen. Medizinische Welt (Stuttgart). 28(1):23-29, 1977.

The literature on the psychotropic effects of hormones is reviewed, and neuropsychopharmacological models employed in the interpretation of such effects are examined. The demonstration of psychotropic effects has been attempted electrophysiologically, through psychological testing, and biochemically. Androgens have been studied for their influence on sexuality, aggressivity, mood, activity, performance, and personality. The correlation of clinical symptoms and diagnostic test results after administration of androgens yields tentative models for future research. Hormonal activation in cases of mood changes (e.g. depressive syndrome) may be measured by subjective scales, EEG, and plasma monoamine oxidase (MAO) levels. Activity, motor and mental performance can be quantified by CNS activity tests and other performance tests, EEG, ergometry, and analysis of STH, cortisol, plasma sodium, testosterone, and other physiological stress factors. Sexuality parameters are established through questionnaires, phallography, and plasma testosterone under sexual stimulation. Various scales and inventories are available for assessment of changes in aggressivity and personality characteristics under the influence of hormones. 49 references.

003871 Hitchens, Emily A. Psychosocial Nursing Department, University of Washington School of Nursing, Seattle, WA 98105 **Helping psychiatric outpatients accept drug therapy.** American Journal of Nursing. 77(3):464-466, 1977.

The role of nurses in community health agencies in helping patients convalescing from a psychotic episode accept the need for medication on a maintenance basis is discussed. Studies are cited to show that most patients who are hospitalized fail to follow their medication schedule after discharge. Nurses counseling discharged patients must work through the feelings and issues surrounding emotional and physical drug dependence. Three issues in followup care are considered: the immediate convalescence after a serious psychosis; the search for another treatment or cure; and the acceptance of a lifestyle change. The success of group therapy in conjunction with drug therapy is described. Two major issues in such groups are: feelings, relationships, and self-perception; and medication. Providing maintenance programs in the community depends on a nurse's knowledge and personal acceptance of a particular medication therapy, based on an understanding of the phases following a psychosis and on various intensitites of group counseling. Compliance is further supported by the nurse who generates a positive attitude toward such patients within the community facility. 8 references.

003872 Hollister, Leo E. no address **Withdrawal from benzodiazepine therapy.** Journal of the American Medical Association. 237(14):1432, 1977.

In a letter to the editor, it is suggested that a report of three cases of "withdrawal psychosis" following abrupt discontinuation of benzodiazepine therapy is a misleading use of the term and that the cases might better be described as "acute brain

syndrome due to drug withdrawal." It is suggested that the psychiatric components in the withdrawal syndromes reported may have been caused by the concomitant use of a phenothiazine in one case, by a concurrent depressive disorder in the second, and by possible concurrent psychomotor seizures in the third case. It is noted that psychotic symptoms have not been prominent in the few withdrawal reactions to benzodiazepines reported. Drugs such as the benzodiazepines that have plasma half-lives from 30 to 96 hours have their own built in tapering effect. Since any CNS depressant may produce withdrawal reactions when use is abruptly discontinued, it is advised that physicians should never discontinue excessively large doses of such drugs suddenly. It is felt that the reported cases serve not only to remind physicians of possible withdrawal reactions from benzodiazepines as well as other drugs but also that the mental reactions reported are not specific to the drugs in question.

003873 Huey, Karen. no address **The chronic psychiatric patient in the community: highlights from a conference in Boston.** Hospital & Community Psychiatry. 28(4):283-290, 1977.

The chronic psychiatric patient in the community and ways of caring for him are discussed. There has been a rapid reduction in the number of individuals resettled in the separate community of long-term psychiatric institutions during the last 25 years. The community mental health center is being used more and more, even for chronic psychotics. It is advocated that many areas should be supported, such as public education about the nature of chronic psychiatric disorders, adequate health and rehabilitational services and adequate means of financial support for each individual to help the community accept the mentally ill. The patient must be viewed not as an isolated individual but as a member of a family, a community and a social system. Crisis intervention, an inexpensive short-term therapy that focuses on solving a particular problem, can offer the immediate help that a person in crisis needs in order to reestablish equilibrium. Work is considered to be a necessary element in the assimilation of former mental patients into normal community life. The success of foster family care is described. A variety of homes should be developed to take care of patients who have rehabilitation potential. Each patient's needs must be assessed and he must be matched to the appropriate home. Antiphyschotic drugs have played a major and essential role in emptying public mental hospitals. Although drugs have had a considerable impact on the deinstitutionalization that has taken place over the last 20 years, administrative and social changes have interacted with pharmacology in a mutually supportive way.

003874 Iuvone, P. Michael; Morasco, Joan; Dunn, Adrian J. Laboratory of Preclinical Pharmacology, NIMH, St. Elizabeth's Hospital, Washington, DC 20032 **Effect of corticosterone on the synthesis of (3H)catecholamines in the brains of CD-1 mice.** Brain Research (Amsterdam). 120(3):571-576, 1977.

The effects of corticosterone on the conversion of 3H-tyrosine into 3H-catecholamine in the brains of endocrinologically intact mice were investigated. The results of the experiments indicate that corticosterone increases the synthesis of norepinephrine. This treatment also increases the relative specific activity of dopamine. The injection of corticosterone had no effect on the level of norepinephrine or dopamine. Corticosterone administration also had no effect on the incorporation of 3H-tyrosine into protein, indicating that the change in norepinephrine turnover was not caused by a generalized increase in cerebral metabolism. Effects of corticosterone on central NE and DA turnovers may be related to some of the behavioral effects of this hormone.

003875 Izumi, Kanji; Motomatsu, Toshiharu; Chretien, Michel; Butterworth, Roger F.; Lis, Martin; Seidah, Nabil; Barbeau, Andre. Clinical Research Institute of Montreal, Montreal, Quebec, Canada **Beta-endorphin induced akinesia in rats: effect of apomorphine and alpha-methyl-p-tyrosine and related modifications of dopamine turnover in the basal ganglia.** Life Sciences. 20(7):1149-1155, 1977.

The effects of apomorphine (APO) and alpha-methyl-p-tyrosine (MT) on beta-endorphin (BE) induced akinesia and related modification of dopamine (DA) turnover in the basal ganglia were studied in rats. BE induced akinesia and loss of corneal reflex in rats. APO fully reversed akinesia and elicited stereotyped behavior; during complete disappearance of akinesia, the corneal reflex was still absent. Pretreatment with MT potentiated the effect of BE on muscle rigidity. BE did not alter the concentration of DA and norepinephrine (NE) in any brain region, but significantly increased the concentrations of 5-hydroxytryptamine in the midbrain. MT decreased DA and NE in the midbrain and striatum and NE in the hypothalamus. Treatment with BE partially corrected the decreased concentrations of DA in the midbrain, and a similar tendency was observed in the striatum; however, BE did not affect the concentrations of NE. Although the results indicate that dopaminergic neurons are involved in the action of BE, effects of the peptide on other neuronal systems should also be considered. 26 references.

003876 Jacobson, Arthur E.; Klee, Werner A.; Dunn, William J. III. Medicinal Chemistry Section, National Institute of Arthritis, Metabolism and Digestive Diseases, NIH, Bethesda, MD 20014 **A quantitative relationship between antinociceptive activity, opiate receptor affinity and lipophilicity.** European Journal of Medicinal Chemistry (Paris). 12(1):49-52, 1977.

The quantitative relationship between antinociceptive activity in mice, opiate receptor affinity in rat brain homogenates, and lipophilicity was determined for 10 structurally diverse analgesics; etorphine, fentanyl, levorphanol, hydromorphone, ketobemidone, methadone, dihydromorphine, morphine, pethidine, and normorphine. Regression analysis showed a quatitative relationship between the antinociceptive activity, as measured by the standard hot plate assay, of the 10 drugs and their receptor affinity and lipophilicity. About 82% of the variance in the antinociceptive activity of the representative compounds from the morphine, methadone, pethidine, 6,14-endoethenoterahydroroipavine and propionamide (fentanyl) families of analgesics was accounted for by a linear combination of the two independent parameters. Neither lipophilicity nor receptor binding affinity alone could be directly related to the antinociceptitive activity of the compounds. 13 references. (Author abstract modified)

003877 Johnson, F. N. Department of Psychology, University of Lancaster, Fylde College, Bailrigg, Lancaster, England **The impact of drug therapy upon psychiatry: a web of paradoxes.** Public Health (London). 91(1):19-22, 1977.

The impact of drug therapy on psychiatry is discussed in terms of three paradoxes. It is argued that the continued success of drug treatment for many psychiatric disorders has led to the strengthening of certain beliefs about the nature of mental illness. First, it has led to an erroneous strengthening of belief in the medical model of psychiatric disorders, the belief that behavioral and cognitive characteristics of a given condition are merely symptoms of an underlying causative agent.

Second, the failure to find a disorder specific pharmacological treatment has led, again erroneously, to a strengthening of belief in a process dysfunction view of mental illness. In each case, the paradox is that these misinterpretations of the findings from drug therapy may well lead to a more effective approach to the question of mental health. An additional paradox is that if the medical model and the process model of mental illness are tenable positions, they are then mutually incompatible. Hope is expressed that long-term results of drug therapy will lead to a more careful conceptual analysis of the viewpoints examined and lay a basis for a unified approach to mental health problems. (Author abstract modified)

003878 Kato, Ryuichi. Research Laboratories, Fujisawa Pharmaceutical Company, 2-Kashima, Yodogawa-ku, Osaka 532, Japan **Drug metabolism under pathological and abnormal physiological states in animals and man.** Xenobiotica (London). 7(1/2):25-92, 1977.

The effects of a wide variety of pathological and abnormal physiological states in both animals and man on drug metabolism are examined. Particular attention is given to sex related differences in metabolism and to the effects of changes in nutritional states on drug metabolism. Several abnormal or pathological states that may affect drug metabolism are discussed, including: liver diseases; heart and kidney diseases; hormonal disturbances; pregnancy; tumor bearing states; adjuvant arthritis; abnormalities in the reticuloendothelial system, spleen and thymus; and states related to environmental factors such as physical stress, irradiation and heavy metal intake. It is concluded that several pathological or abnormal physiological states alter the microsomal drug metabolizing enzymes. In rats, microsomal drug metabolizing enzyme activity is higher in males than in females through androgen action which is readily impaired by certain pathological states. It is therefore suggested that female rats be used in the evaluation of pathological states on hepatic microsomal drug metabolizing enzymes. 459 references.

003879 Kemp, Katherine; Lion, John R.; Magram, Gary. Inst. of Psychiatry and Human Behavior, 645 W. Redwood Street, Baltimore, MD 21201 **Lithium in the treatment of a manic patient with multiple sclerosis: a case report.** Diseases of the Nervous System. 38(3):210-211, 1977.

The effect of lithium in a female multiple sclerosis patient with symptoms of agitated depression is described in a case report. Prior to lithium administration, the patient had been given ACTH during periods of exacerbation of symptoms. Following consideration of steriod psychosis, the patient was treated with lithium carbonate 300mg tid. Manic behavior disappeared completely and the patient was maintained on lithium. Subsequent to the recurrence of diplopia, the patient was treated with ACTH and an increased dosage of lithium. The patient showed no mania or hypomania while followed on an outpatient basis for over 4 months. It is suggested that lithium may have played some role in the treatment of a bipolar affective condition which was secondary to the multiple sclerosis or primary in etiology. It is suggested that a patient with organic brain damage placed on lithium should be closely monitored for toxic effects. 10 references.

003880 Kuczenski, Ronald; Schmidt, Dennis; Leith, Nancy. Department of Pharmacology, Vanderbilt University, Nashville, TN 37217 **Amphetamine-haloperidol interactions in rat striatum: failure to correlate behavioral effects with dopaminergic and cholinergic dynamics.** Brain Research (Amsterdam). 126(1):117-129, 1977.

The effects of amphetamine (AM) on behavioral effects and dopaminergic and cholinergic dynamics and its interaction with haloperidol (HP) in rat striatum were studied. Administration of AM produced hyperactivity and decreased dopamine (DA) biosynthesis, both of which were blocked by HP. Increased dosage of AM produced stereotypy, further decreased DA biosynthesis and caused a decrease in choline uptake, consistent with stimulation of DA receptors. However, while pretreatment with HP completely blocked the stereotypy induced by AM, it failed to reverse the effects of this dose on either DA biosynthesis or choline uptake. The data suggest that either AM affects striatal dopaminergic and cholinergic parameters by a mechanism independent of HP sensitive receptors, or the stereotypy produced by high doses of AM are not related to striatal dopaminergic and cholinergic functions. 55 references. (Author abstract modified)

003881 Langer, Gerhard; Ahn, Ho Sam; Perel, James M.; Makman, Maynard H.; Sachar, Edward J. Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY 10032 **No effects of quaternary neuroleptics on human prolactin and adenylcyclase.** Lancet (London). No. 8009:493, 1977.

In a letter to the editor, it is suggested that quaternary ammonium salts of neuroleptic drugs may be a valuable tool for evaluating possible psychotropic effects of neuroleptics which might be triggered by the action of the drugs outside the blood/brain barrier since quaternary ammonium salts cannot penetrate the blood/brain barrier in significant amounts. When compared in behavioral tests in rats tertiary, conventional counterparts and quaternary neuroleptics are roughly equivalent. It is suggested that this does not appear to be the same in man. It was found that in contrast to their tertiary analogs, the quaternary neuroleptics did not release human prolactin, nor did they block dopamine sensitive adenylcyclase activity in the cebus monkey homogenates. Based on these findings, it is believed that further investigations aimed at clarifying the pharmacological effects of quaternary neuroleptics as compared with those of their tertiary analogs should be conducted.

003882 Lawson, Allan H. Prisoners' Rights Council, Philadelphia, PA **/Testimony by an ex-convict against medical experimentation in prisons./** An ex-convict testifies. Hastings Center Report. 7(1):14, 1977.

In testimony before the National Commission for the Protection of Human Subjects of Behavioral and Biomedical Research, arguments in favor of a moratorium on human experimentation in Pennsylvania are given. Two schools of thought among prisoners are described: one group wanted continuation of testing so they could earn money for bail, attorneys, and families; another was suspicious that Black prisoners were being subjected to genocidal practices. Under questioning, it is conceded that working in a stamping factory as an alternative to participation in biomedical research may lead to deafness from noise; still, such work is preferable to subjection to medical experimentation. In answer to a further question, it is said that two schools of thought probably still exist among prisoners even after the moratorium.

003883 Lee, R.; Spencer, P. S. J. Applied Pharmacology Laboratories, Welsh School of Pharmacy, UWIST, Cardiff, Wales **Andidepressants and pain: a review of the pharmacological data supporting the use of certain tricyclics in chronic pain.** Journal of International Medical Research (Northampton). 5(Suppliment 1):146-163, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the pharmacological data supporting the use of certain tricyclics generally used as antidepressants on chronic pain is reviewed. The pharmacological properties of centrally acting analgesics and the tricyclic antidepressants are examined and compared to establish a scientific basis for the observed clinical effects of the tricyclics. Opiates and tricyclic antidepressants share a number of pharmacological properties including activity in animal tests for antidepressant and analgesic activity. In doses which alone were not analgesic, clomipramine potentiated while maprotiline attenuated the analgesic activity of single doses of morphine in laboratory animals. However, when morphine and a tricyclic agent were given repeatedly over several days, clomipramine enhanced or accelerated the onset of morphine tolerance, whereas maprotiline delayed tolerance. It is concluded that there is much experimental data to support the belief that tricyclics such as clomipramine may be useful in chronic clinical pain. Where an opiate is being administered chronically (for example in terminal pain) the concomitant administration of maprotiline may delay onset of tolerance. 19 references. (Journal abstract modified)

003884 Levine, Candace; Dang, Jagdish C. Department of Psychiatry, St. Joseph's Hospital and Medical Center, Paterson, NJ **Psychopharmacology and social work skills.** Social Casework. 58(3):153-158, 1977.

A seminar, held at St. Joseph's Hospital and Medical Center, Paterson, NJ, in 1975, concerned with the increased responsibilities of psychiatric social workers who are called upon to help clients use psychotropic medications is reported. Emphasis was on the need for a clearer sense of their responsibilities and limitations in this field. Areas in which the social worker should be knowlegeable include: 1) individual patients' medical history, pertinent examinations, and tests; 2) the different categories of psychiatric medications, e.g. sedatives, soporific major tranquilizers, nonsoporific major tranquilizers, antidepressants and minor tranquilizers; and 3) electroconvulsive therapy, insulin therapy, and psychosurgery. It is concluded that the understanding of different mental health skills, including psychopharmacology, leads to the most informed and effective team approach to patient care. 9 references.

003885 Lipton, Morris A. Child Development Research Institute, School of Medicine, University of North Carolina, Chapel Hill, NC 27514 **Pharmacological research and the psychoses: an overview.** In: Research on disorders of the mind: progress and prospects. Rockville, MD, NIMH, 1977. 54p. (p. 24-25) $1.20.

A condensation of a paper presented at the 100th meeting of the National Advisory Mental Health Council held September, 1975 on Research on Disorders of the Mind reviews pharmacological research relating to the psychoses. The interaction between psychopharmacology and the basic sciences dates back to the discovery of the psychotropic drugs. It is stated that improvement in the treatment of schizophrenia awaits the development of better drugs, and the combination of various drugs is a promising approach to treatment of schizophrenia. It is asserted that there has been virtually no progress in identification of environmental factors in the psychoses.

003886 no author. no address **General practitioners' prescribing habits for patients with depression.** Current Therapeutics. 18(1):51-53, 1977.

General practitioners' prescribing practices for antidepressant and psychotherapeutic drugs were surveyed. Seventeen psychiatrists and 227 general practitioners were administered an eight question examination covering fundamental material on drug treatment of depressive illness. Half of the questions showed significant differences between the two groups' responses. It was shown that general practitioners tend to be cautious in prescribing tricyclics (imipramine, amitriptyline) and prescribe lower dosages than psychiatrists although both groups tend to discontinue therapy prematurely. Emphasis is made of the importance of diagnostically distinguishing between depressive neurosis, reactive depression, and endogenous depression before prescribing medication, shock therapy, or psychotherapy.

003887 Noone, J. F. no address **Psychotropic drugs and migraine.** Journal of International Medical Research (Northampton). 5(Supplement 1):66-71, 1977.

At a symposium held at Rabat, Malta, in November, 1976, the effect of psychotropic drugs on the incidence and differential diagnosis of migraine is discussed. The use of clomipramine in the prophylaxis of migraine is considered and the results of a pilot study presented. The problems which arise in the organization of clinical trials of migraine prophylaxis and hypotheses for the possible mode of action of clomipramine and other psychotropic drugs in the prevention of migraine are discussed. 7 references. (Journal abstract modified)

003888 Overall, John E.; Henry, B. W.; Woodward, J. Arthur. Department of Psychiatry, University of Texas Medical Branch, Galveston, TX 77550 **Decisions about drug therapy -- V. Models derived from diagnostic frequency patterns.** Journal of Psychiatric Research (Oxford). 13(2):77-89, 1977.

Methodology for analysis of diagnostic frequency patterns in drug prescription data for purposes of understanding similarities and differences in clinical conceptions of actions of the drugs is proposed. The method of multidimensional scaling employed in the investigation produces a structural model of decision-making by the physicians whose drug prescription practices were monitored in 1469 cases. Three different methods for analysis of such data are compared. Analyses reveal differences in clinical conceptions of drugs within the major classes as well as between them. It is concluded that patterns of drug prescriptions can provide valuable insights into subtle differences in clinical conceptions of the drug actions. 7 references. (Author abstract modified)

003889 Perlman, Barry; Hogben, George. Dept. of Psychiatry, Mt. Sinai School of Medicine, 100th Street and Fifth Avenue, New York, NY 10029 **Effects of changes in standing medication distribution times on PRN drug use.** Diseases of the Nervous System. 38(3):181-185, 1977.

Medication use on an inpatient psychiatric unit was studied to determine the effect of changes in standing distribution time on as needed (prove nata, prn) administration. Significantly fewer prn doses of tranquilizers and hypnotics were requested when standing medications were distributed at 8am, 12 noon, 4pm and 9pm rather than at 10am, 2pm, 6pm and 10pm. Distribution of analgesics was not affected. It is suggested that the time of distribution of standing medication doses may be considered an aspect of the placebo effects of the drugs. The differences in prn tranquilizer consumption in the two periods studied suggest that the patients' sense of symptom amelioration is influenced by distribution schedule as well as total milligram amounts of drugs given. 14 references. (Author abstract modified)

003890 Powell, Barbara J.; Othmer, Ekkehard; Sinkhorn, Charlotte. VA Hospital, Lexington, KY 40507 **Pharmacological aftercare for homogenous groups of patients.** Hospital and Community Psychiatry. 28(2):125-127, 1977.

A group therapy pharmacological aftercare program aimed at evaluating the effectiveness of the pharmacotherapy and encouraging discharged Veterans Administration psychiatric patients to continue medication is described. Recently discharged patients who have indicated good response to pharmacotherapy are assigned to homogenous groups: 1) fluphenazine decanoate group for schizophrenics; 2) lithium carbonate group for bipolar depressives; and 3) affective disorders group for unipolar depressives. Each group meets for 2 hour sessions monthly for a period of 8 to 12 months with a multidisciplinary team. Group objectives include educating patients on the nature of their disorder and its management, providing psychological support and providing positive reinforcement for desirable behaviors. Patients are informed of possible side-effects and the importance of continuing medication, and the efficacy of the medication is periodically assessed using a symptom rating scale. Of 85 patients attending the first 12 month group period, attendance was 87.3%; and rehospitalization was necessary for only 20%, of which 50% resulted from failure to continue medication. It is concluded that group therapy presents an effective and efficient means for providing pharmacological aftercare. 4 references.

003891 Regalado, R. G. no address **Clomipramine (Anafranil) and musculo-skeletal pain in general practice: a pilot, open, non-comparative study of long-standing, rheumatic pain.** Journal of International Medical presearch (Northampton). 5(Supplement 1): 72-77, 1977.

At a symposium held at Rabat, Malta, in November, 1976, an open, noncomparative study of the treatment of long standing rheumatic pain by clomipramine was made with forty six patients. The duration of the trial was 56 days during which patients received daily doses of either 10mg or 25mg of clomipramine. Assessments were made at fortnightly intervals. Patients were assessed for pain using a visual analogue scale, analgesic requirement, joint pain, other pain and morning stiffness. At the completion of the study patients were asked whether the addition of clomipramine to their treatment was better, the same, or worse than no additional treatment. Twenty one patients (57%) felt that it was better, four felt that it was the same, and twelve said that it was worse. The doctor also similarly recorded his preference at the end of the trial. In twenty two cases (60%) the doctor felt it was better, in eight that there was no difference and in seven that it was worse. There was no difference between the 10mg and the 25mg regime. It is suggested that better control of rheumatic symptoms can be achieved in some patients by the addition of small daily doses of clomipramine to their standard antirheumatic therapy. 6 references. (Journal abstract modified)

003892 Reilly, Peter P.; Cohen, Lauren B. 950 Smith Street, Providence, RI 02908 **Lithium as an anti-depressant: discoveries through clinical observations.** Rhode Island Medical Journal. 60(3):131-138, 1977.

The use of lithium to treat endogenous depression is discussed, citing the recent advances in knowledge of the mechanism of action, clinical studies of use, administration and dosimetry of lithium carbonate, contraindications, side-effects, toxicity, and case histories. Lithium is a relatively safe and effective medication for endogenous depression. It can be used alone, in which case it acts quickly or in combination with tricyclics enhancing their antidepressant effects. It is suggested that more research is needed to understand its mechanism of action and its long-term effectiveness. 11 references.

003893 Rosin, Arnold J. Harzfeld Hospital, Gedera, Israel **The physical and behavioural complex of dementia.** Gerontology (Basel). 23(1):37-46, 1977.

An inquiry into the physical and behavioral problems of patients hospitalized for dementia was presented. Dementia is a syndrome comprising intellectual failure of memory, thinking, and judgement, and deterioration in personality and social functioning. Eighty one patients (70-80-years-old) were studied over a period of 3 years and a comparison was made between 38 Ss with idiopathic (Alzheimer's) dementia, and the others most of whom suffered from focal cerebral arteriosclerosis of Parkinson's disease with dementia. Nursing difficulties ranged from immobility in some patients to wandering about in others, especially in the Alzheimer's group. Behavior disturbances, shouting, incontinence, and degenerate habits were found in a high proportion and there was a 15% incidence of fractures. The mainstays of treatment were tranquillizing drugs, used only when necessary, and in minimal quantities, and simple occupational activity. 9 references. (Author abstract modified)

003894 Roth, W. T.; Tinklenberg, J. R.; Kopell, B. S. Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305 **Ethanol and marihuana effects on event-related potentials in a memory retrieval paradigm.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 42(3):381-388, 1977.

The effects of ethanol and marihuana intoxication on event related potentials in a memory retrieval paradigm were studied in 12 men. The men performed the Steinberg memory retrieval task and simultaneously, the electroencephalogram was recorded from the vertex to linked ears and the electrooculogram from leads above and below the right eye. N1 was defined as the minimum in the latency range 70-150 msec from the warning tone, P2 as the maximum from N1 to 200 msec, and P3 as the maximum in the range 280-380 msec. There were no drug effects on N1 in the evoked potential to the warning tone, but P3 amplitude was smaller under tetrahydrocannabinol (THC) and ethanol than under placebo. The contingent negative variation (CNV) amplitude in the interval between the warning tone and the test digit showed no drug effects; however, the latency of 50% resolution of the CNV was longer under THC than placebo. THC also increased the reaction time for each set size by about 74 msec above the values for ethanol and placebo, the latter two not differing significantly. Set size affected N1 and P3 amplitudes and latencies and CNV amplitude, as well as 50% CNV resolution latency and reaction time, but there were no drug times set size interactions. 23 references. (Author abstract modified)

003895 Schoolar, Joseph C. Baylor College of Medicine, Houston, TX 77030 **Mood-active agents in depression.** In: Fann, W., Phenomenology and treatment of depression. New York, Spectrum, 1977. 350 p. (p.251-264).

In a paper presented to a symposium on Phenomenology and Treatment of Depression held at Baylor University in December, 1975, psychotropic medications used in the treatment of depression are examined briefly with a focus on the role of the psychopharmacologist. Three current pharmacological approaches to the treatment of depression -- the tricyclic antidepressants, monoamine oxidase inhibitors, and lithium -- are discussed. The continuing controversy over the precise

roles and value of pharmacological therapy in depression, with some studies showing it to be valuable and other studies showing otherwise, is noted. 14 references.

003896 Schroeder, Nancy H.; Caffey, Eugene M., Jr.; Lorei, Theodore W. Veterans Administration Central Office (152C2), 810 Vermont Avenue, Washington, DC 20420 **Antipsychotic drug use: physician prescribing practices in relation to current recommendations.** Diseases of the Nervous System. 38(2):114-116, 1977.

The prescribing practices for psychotherapeutic drugs in a sample of patients from 42 Veterans Administration hospitals was compared to recommendations available in current literature. Generally, the results showed moderate differences between the actual physician practices and those recommended in the guidelines. The most significant differences were in polypharmacy, use of antiparkinson drugs, dosage levels, and drug holidays. The use of once or twice a day schedules and the administration of a major portion of the dose at night were much closer to the recommendations. The adequacy of guidelines and current dissemination of research findings is questioned. 4 references. (Author abstract modified)

003897 Seldrup, J. Research and Medical Department, CIBA-GEIGY (UK) Limited, Macclesfield, Cheshire, England **Comparison between physician and patient completed visual analogue scales.** Journal of International Medical Research (Northampton). 5(Supplement 1):55-60, 1977.

At a symposium held at Rabat, Malta, in November, 1976, a comparison was made between physician and patient independently completed visual analogue scales in a general practitioner trial in which patients were treated with various doses of clomipramine. A regression technique is described to deal with the comparison between patient and doctor completed scales. It is suggested that this method is more informative than just giving correlations between ratings. It is shown that for the two target symptoms, depression and anxiety, the agreement between patient and doctor ratings is poor, particularly at the beginning of the study. The best results are obtained for initial sleep, appetite, and libido. Some explanations for these findings are offered, and further researches of the visual analogue scale are suggested. 10 references. (Journal abstract modified)

003898 Senay, Edward C.; Dorus, Walter; Goldberg, Faye; Thornton, William. Department of Psychiatry, University of Chicago, 950 E. 59th St., Chicago, IL 60637 **Withdrawal from methadone maintenance: rate of withdrawal and expectation.** Archives of General Psychiatry. 34(3):361-367, 1977.

To study the effects of expectation and rate of dose decrease in the course of withdrawal, 127 patients successfully maintained on methadone hydrochloride were randomly assigned to one of the following four groups and studied for 30 weeks: 1) known maintenance patients were maintained on methadone under open conditions; 2) blind maintenance patients were maintained on methadone under double-blind conditions; 3) rapid withdrawal patients were withdrawn under double-blind conditions at a rate of 10% of initial dose per week; and 4) gradual withdrawal patients were withdrawn under double-blind conditions at rate of 3% of initial dose per week. Differences in dropout rates, illicit drug use, symptoms scores, and requests for study interruption indicate that withdrawal from methadone maintenance should be carried out at approximately 3% of initial dose per week. Better patient preparation also is indicated to reduce the effects of expectation. 13 references. (Author abstract)

003899 Smith, Mickey C. Department of Health Care Administration, University of Mississippi, School of Pharmacy, University, MS 38677 **Appeals used in advertisements for psychotropic drugs: an exploratory study.** American Journal of Public Health. 67(2):171-173, 1977.

The appeals used in advertisements for psychotropic drugs appearing in 60 medical journals were studied in order to determine their accuracy and source of influence. Four pharmacy students rated the illustrations, headlines, and text separately. The data indicate that the illustration, a major attention getting device, is often associated with a nonrational appeal. If the physician's attention is held long enough to read the headline and text then the appeal becomes more rational. It is concluded that the advertisements encourage "at a glance" emotional appeal. 8 references.

003900 Starr, Dorothy A. Department of Psychiatry and Neurology, Walter Reed Army Medical Center, Washington, DC 20012 **Psychopharmacology.** Journal of the American Medical Women's Association. 32(1):10-14, 1977.

Psychopharmacotherapy and the psychotropic drugs important in the management of mental illnesses were discussed in a paper presented at the 1976 meeting of the American Medical Women's Association. General guidelines for the prescription of psychotropic drugs include: 1) know the patient and define the target symptoms; 2) gain knowledge and experience with the use of one of each type of psychotropic drug; 3) give an adequate dosage and allow adequate time with antipsychotics and antidepressants; 4) be wary of habituation with antianxiety drugs; and 5) consider treatment for depression or functional psychoses in the elderly. Dosages, physiological and behavioral actions, and side-effects for the major antianxiety, antipsychotic, and antidepressive agents are described. Therapeutic uses of lithium also are examined. Cautions against polypharmacy and the overmedication of women, as well as the undermedication of the elderly, are presented.

003901 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Reserpine: mirror image of the antidepressants.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 43-46).

The possibility that reserpine is a mirror image of the antidepressants in its psychopathological and biochemical effects is discussed. Research has indicated that reserpine reduces the effective concentrations of monoamines (MA) at the central receptors by inhibiting MA uptake and/or storage synaptic vesicles, resulting in increased degradation of the MAs by monoamine oxidase and a consequent decrease in MA concentration. It is suggested this that effect is probably responsible for the sedative effect of reserpine in test animals. It is uncertain, however, whether a particular MA plays a key role in this respect, and if so, which one is involved. A correlation is also suspected between reserpine induced depression and MA depletion in humans. Arguments in favor of this correlation are mainly derived from animal experiments, as little pertinent systematic research which might verify this theory has been performed in human patients.

003902 van Praag, H. M. Department of Biological Psychiatry, Psychiatric University Clinic, Groningen, The Netherlands **Tricyclic antidepressants and central monoamine metabolism.** In: van Praag, H., Depression and schizophrenia. New York, Spectrum, 1977. 260 p. (p. 33-38).

Studies conducted in animals (rats and rabbits) and in humans of the effects of tricyclic antidepressants on the metabolism of central monoamines are reviewed. It has been found that tricyclic antidepressants: 1) potentiate the peripheral effects of exogenous noradrenaline (NA) as well as the central effects of substances whose activity is related to increased NA activity; 2) reduce the uptake of NA into noradrenergic nerve endings; 3) alter the degradation pattern of NA so that methylated products are increased and deaminated products are decreased; 4) potentiate the central effects of 5-hydroxytryptophan which are mediated via central serotonin (5-hydroxytryptamine, 5-HT); 5) in vitro, inhibit the uptake of 5-HT into human blood platelets as well as into brain tissue slices and isolated nerve endings; 6) in vivo, inhibit the uptake of 5-HT after injection into the lateral ventricle; 7) decrease the turnover rate of both 5-HT and NA in the brain; and 8) apparently do not affect dopamine uptake or metabolism. Various tricyclic antidepressants have differential effects on the uptake of 5-HT and NA. Secondary amines, such as protriptyline and desmethylimipramine, are potnet inhibitors of NA uptake and exert relatively little influence on 5-HT uptake. The reverse is true for tertiary amines such as imipramine, amitriptyline, and chlorimipramine. It is stated that although numerous findings support the hypothesis that tricyclic antidepressants inhibit the uptake of NA and 5-HT into noradrenergic and serotonergic neurons, there are no unequivocal arguments in favor of a correlation between the biochemical and therapeutic effects of these drugs.

003903 Wyatt, Richard Jed; Torgow, Joan S. Laboratory of Clinical Psychopharmocology, Division of Special Mental Health Research, Saint Elizabeth's Hospital, Washington, DC 20032 **A comparison of equivalent clinical potencies of neuroleptics as used to treat schizophrenia and affective disorders.** Journal of Psychiatric Research (Oxford). 13(2):91-98, 1977.

In a preliminary attempt to examine the neuroleptics' specificity with respect to diagnosis, equivalent clinical potencies of neuroleptics as used to treat schizophrenia and affective disorders were compared by a review of the literature. Equivalent clinical potencies of drugs found to be equally efficacious within each diagnostic category were computed and compared. This correlation across disorders was found to be high and was attributed to the possibility that the drugs effect their treatment through a system peripheral to one or both core abnormalities. It is proposed that the brain dopamine systems are the affected area. 68 references. (Author abstract modified)

003904 Youdim, M. B. H. University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford OX2 6HE, England **Factors influencing the deamination and functional activity of biogenic monoamines in the central nervous system.** In: Gershon, E., The impact of biology on modern psychiatry. New York, Plenum, 1977. 276 p. (p. 125-136).

In a paper presented at a symposium on the impact of biology on modern psychiatry conducted to honor the 80th anniversary of the Jerusalem Mental Health Center Ezrath Nashim in Jerusalem, Israel in December, 1975, studies using monoamine (MAO) inhibitors to investigate factors influencing the deamination and functional activity of biogenic monoamines are reviewed. Among the topics discussed are: 1) the role of MAO in the central nervous system; 2) the multiple forms of MAO and their substrate specificities and inhibitor sensitivities, e.g. type A MAO is selectively inhibited by clorgyline and deaminates serotonin (5-hydroxytryptamine, 5-HT), noradrenalin, and octopamine, while type B MAO is selectively inhibited by deprenil and deaminates phenylethylamine, benzylamine, kynuramine, and tryptamine, and both forms of MAO deaminate dopamine (DA); 3) the involvement of inhibition of type A MAO and/or type B MAO resulting in elevations of brain levels of 5-HT and/or DA in the production of tyramine induced hyperactivity in rats; 4) the view that multiple forms of MAO may act as an integrated enzyme system having in vivo properties different from the individual enzyme forms seen in vitro; 5) biological factors in humans which can affect the activity of MAO, such as estrous cycle, growth, naturally occurring steroids, and dietary influences such as iron intake; 6) the possibility that disturbances in MAO function are involved in schizophrenia and unipolar depression; 7) the question of whether changes in blood platelet MAO activity can be used as an indication of similar changes in brain MAO activity; 8) the possible clinical usefulness of selective MAO inhibitors such as deprenil; 9) the use of radiolabeled irreversible MAO inhibitors to study the active site of membrane bound mitochondrial MAO; and 10) the determination of mol to mol binding of radiolabeled MAO inhibitors to MAO as an indication of tissue enzyme concentration. 46 references.

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